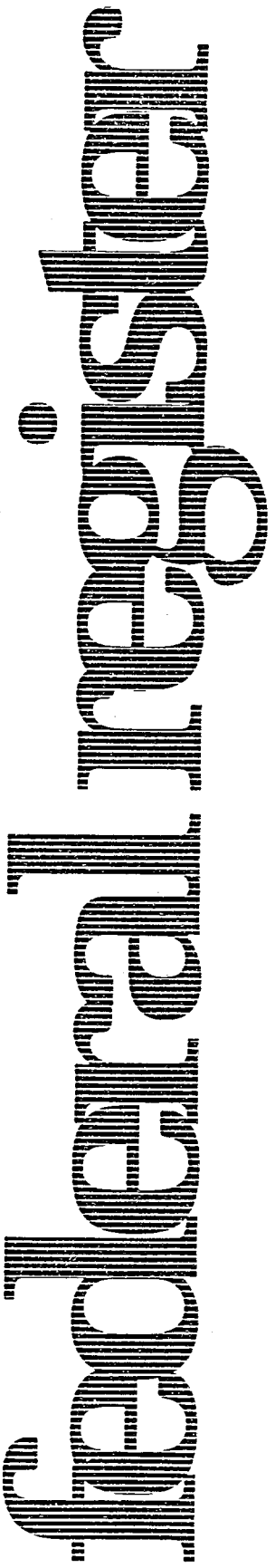
TAB 1 Federal Register Notice: Tentative Final Monograph for OTC Healthcare Antiseptic Drug Products - June 17, 1994

The Agency's evaluation of new drug products and monograph ingredients relies on testing and effectiveness criteria proposed by the Agency in its public rulemaking for OTC healthcare antiseptic drug products (i.e., healthcare personnel handwashes, surgical hand scrubs, and patient preoperative skin preparations).

- In this notice, FDA amends the TFM to establish subpart E of part 333, establishment of a monograph for OTC healthcare antiseptic drug products. This category is generally intended for use by health professionals and includes healthcare personnel hand washes, surgical hand scrubs, and patient preoperative skin preparation.

- pages 31430-31433, discusses comments regarding testing issues

- page 31441, begins FDA's proposal on new subpart E – Healthcare Antiseptic Drug Products, which include the following:
  - § 333.403 Definitions.
  - § 333.410 Healthcare personnel handwash active ingredients.
  - § 333.412 Patient preoperative skin preparation active ingredients.
  - § 333.414 Surgical hand scrub active ingredients.
  - § 333.450 Labeling of healthcare antiseptic drug products.
  - § 333.455 Labeling of healthcare personnel handwash drug products.
  - § 333.460 Labeling of patient preoperative skin preparation drug products.
  - § 333.465 Labeling of surgical hand scrub drug products.
  - § 333.470 Testing of healthcare antiseptic drug products.
    page 31445, effectiveness testing of surgical hand scrub.
    page 31448, effectiveness testing of healthcare personnel handwash.
    page 31450, effectiveness testing of patient preoperative skin preparation.



Friday
June 17, 1994

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 333 and 369

Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 333 and 369

[Docket No. 75N-183H]

RIN 0905-AA06

Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of an amended tentative final monograph that would establish conditions under which over-the-counter (OTC) topical health-care antiseptic drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking to amend the previous notice of proposed rulemaking on topical antimicrobial drug products (see the Federal Register of January 6, 1978, 43 FR 1210) after considering the public comments on that notice and other information in the administrative record for this rulemaking. FDA is also requesting data and information concerning the safety and effectiveness of topical antimicrobials for use as hand sanitizers or dips. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for an oral hearing on the proposed regulation before the Commissioner of Food and Drugs by December 14, 1994. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 180 days for comments and objections instead of the normal 60 days. New data by June 19, 1995. Comments on the new data by August 17, 1995. Written comments on the agency's economic impact determination by December 14, 1994.

ADDRESSES: Written comments, objections, new data, or requests for an oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

SUPPLEMENTARY INFORMATION: In the Federal Register of September 13, 1974 (39 FR 33103), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC topical antimicrobial drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Antimicrobial I Drug Products (Antimicrobial I Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by November 12, 1974. Reply comments in response to comments filed in the initial comment period could be submitted by December 12, 1974. In response to numerous requests, the agency issued a notice in the Federal Register of October 17, 1974 (39 FR 37066) granting an extension of the deadline for comments until December 12, 1974, and for reply comments until January 13, 1975.

In the Federal Register of January 6, 1978 (43 FR 1210), FDA published, under § 330.10(a)(7), a notice of proposed rulemaking to establish a monograph for OTC topical antimicrobial drug products, based on the recommendations of the Antimicrobial I Panel and the agency's response to comments submitted following publication of the advance notice of proposed rulemaking. Interested persons were invited to submit objections or requests for oral hearing by February 6, 1978. In response to numerous requests to extend the time period for submitting objections or requests for oral hearing, the agency issued a notice in the Federal Register of February 3, 1978 (43 FR 4637) granting an extension of the deadline to March 6, 1978. During this time period, the agency received 6 petitions that requested reopening the administrative record and 11 requests for an oral hearing. In a notice published in the Federal Register of March 9, 1979 (44 FR 13041), the agency deferred action on the requests for a hearing, but granted the petitions to reopen the record to allow interested persons to submit comments and any new or additional data by June 7, 1979, and reply comments by July 9, 1979. FDA also stated its intent to publish an updated (amended) tentative final monograph based on the review and evaluation of new submissions and a reevaluation of existing data.

In a notice published in the Federal Register of October 26, 1979 (44 FR 61609), the agency again reopened the administrative record for the submission of new data by March 26, 1980, and for comments on the new data by May 27, 1980. This action was taken to permit manufacturers to submit the results of testing to FDA as expeditiously as possible prior to establishment of a final monograph.

Subsequent to the June 7, 1979, closing date for the submission of new data, and prior to the October 26, 1979, reopening of the administrative record, data and information were submitted to FDA. In a notice published in the Federal Register of March 21, 1980 (45 FR 18398), the agency advised that it had reopened the administrative record for OTC topical antimicrobial drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record on the tentative final monograph had officially closed on March 6, 1978. The agency concluded that any new data and information filed prior to March 21, 1980, should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In a notice published in the Federal Register on January 5, 1982 (47 FR 436), the agency advised that it had again reopened the administrative record for OTC topical antimicrobial drug products to allow for consideration of the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) on mercury-containing drug products. Interested persons were invited to submit comments by April 5, 1982, and reply comments by May 5, 1982. FDA stated that the proceeding to develop a monograph for mercury-containing drug products would be merged with the general proceeding to establish a monograph for OTC topical antimicrobial drug products.

In a notice published in the Federal Register on May 21, 1982 (47 FR 22324), the agency advised that it had again reopened the administrative record for OTC topical antimicrobial drug products to allow for consideration of the recommendations of the Miscellaneous External Panel on alcohol drug products. Interested persons were invited to submit comments by August 19, 1982, and reply comments by September 20, 1982. The notice stated that the proceeding to develop a monograph for alcohol drug products would be merged with the general proceeding to establish a monograph for OTC topical antimicrobial drug products.

In the Federal Register of September 7, 1982 (47 FR 39406), FDA issued a notice to reopen the administrative record for OTC topical antimicrobial drug products to allow for consideration

of the Miscellaneous External Panel's recommendations on topical antimicrobial drug products used for the treatment of diaper rash. The agency discussed topical antimicrobial active ingredients for this use in the **Federal Register** of June 20, 1990 (55 FR 25246).

In accordance with § 330.10(a)(10), the data and information considered by the Panels were put on public display in the Dockets Management Branch (address above), after deletion of a small amount of trade secret information. In response to the previous tentative final monograph and the advance notice of proposed rulemaking for mercury-containing drug products and the advance notice of proposed rulemaking for alcohol drug products, 4 drug manufacturers' associations, 44 drug manufacturers, 1 medical device manufacturer, 1 drug distributor, 2 medical schools, 2 research laboratories, 1 law firm, and 1 consulting firm submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** of September 13, 1974 (39 FR 33103), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (§ 330.10). Similarly, the notice of proposed rulemaking, which was published in the **Federal Register** of January 6, 1978 (43 FR 1210), was designated as a "tentative final monograph." The present document is also designated as a "tentative final monograph." The legal status of each tentative final monograph, however, is that of a proposed rule. The present document is a reproposal regarding health-care antiseptic drug products.

This antimicrobial rulemaking is broad in scope, encompassing products that may contain the same active ingredients, but are labeled and marketed for different intended uses. For example, one group of products is primarily used by consumers for "first aid" and includes skin antiseptics, skin wound cleansers, and skin wound protectants. Another group of products, antiseptic handwashes, are used by consumers on a more frequent, even daily, basis and includes products for personal use in the home, such as when caring for invalids and during family illness. A third group of products is generally intended for use by health professionals and includes health-care personnel handwashes, patient preoperative skin preparations, and surgical hand scrubs.

In order to expedite the completion of the first aid section of the antimicrobial monograph, the agency published a separate tentative final monograph for these products in the **Federal Register** of July 22, 1991 (56 FR 33644). The non-first aid uses of topical antimicrobials, now identified as "health-care antiseptics," are addressed in this document. Although the amended tentative final monographs for first-aid antiseptics and health-care antiseptics are being published separately, both categories will eventually be included under part 333 (21 CFR part 333).

The agency also has decided that OTC topical antimicrobial and topical antibiotic drug products should be included within the same monograph. Although an advance notice of proposed rulemaking to establish a monograph for OTC topical antibiotic drug products was published under part 342 (21 CFR part 342) on April 1, 1977 (42 FR 17642), the final monograph for those products was issued on December 11, 1987 (52 FR 47312) as a new subpart of the OTC topical antimicrobial monograph, part 333, subpart B—Topical First Aid Antibiotic Drug Products. Subpart A will cover first aid antiseptic drug products; subpart C will cover antifungal drug products; subpart D covers acne drug products; and new subpart E will cover health-care antiseptic drug products.

In this tentative final monograph (proposed rule) to establish subpart E of part 333, FDA states its position on the establishment of a monograph for OTC health-care antiseptic drug products. This document addresses only those comments and data concerning the previous antimicrobial tentative final monograph that are related to "non-first aid uses," including products for personal use in the home and products used by health-care professionals.

This proposal constitutes FDA's reevaluation of the January 6, 1978 tentative final monograph based on the comments received and the agency's independent evaluation of the Miscellaneous External Panel's reports on OTC alcohol and mercury-containing drug products and the comments received. The following sections of the January 6, 1978 tentative final monograph for topical antimicrobial drug products are being addressed in this document: §§ 333.1, 333.3, 333.30, 333.50, 333.85, 333.87, 333.97, and 333.99. The following sections of the advance notice of proposed rulemaking for alcohol drug products are being addressed in this document: §§ 333.55 and 333.98. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them. (See section I.)

The OTC drug procedural regulations (21 CFR 330.10) provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA does not use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage. In place of Category I, the term "monograph conditions" is used; in place of Categories II and III, the term "nonmonograph conditions" is used. This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application (hereinafter called application). Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC topical antimicrobial drug products (39 FR 33103), the agency suggested that the conditions included in the monograph

(Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture. The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of January 7, 1972 (37 FR 235) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments and Reply Comments

A. General Comments

1. Two comments contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. One comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464 at 9471 to 9472), and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association v. Weinberger*, 512 F.2d 688, 696 to 698 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers v. FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), aff'd, 637 F.2d 887 (2d Cir. 1981).)

2. One comment pointed out that under "Subpart B—Active Ingredients" of the tentative final monograph, no CFR part number was assigned to the category "skin antiseptic." However, part numbers were assigned to other categories without any Category I ingredients, with the term "reserved" in parentheses. The comment requested that this omission be corrected in the amended tentative final monograph.

The omission pointed out by the comment was an oversight. However, it is no longer necessary to assign a CFR part number to the category "skin antiseptic," because skin antiseptics have been included in broader categories identified as first aid antiseptics in the amended tentative final monograph for first aid antiseptics (56 FR 33644) and as health-care antiseptics in this tentative final monograph. (See section I.B., comment 3.) All Category I first aid antiseptic and health-care antiseptic active ingredients have been listed in the amended tentative final monograph under subpart A and subpart E, respectively.

B. General Comments on Antimicrobials

3. A number of comments objected to the Panel's recommendation for separate statements of identity in the labeling of products containing the same antimicrobial active ingredient. As an example, several comments noted that povidone-iodine has several professional uses (health-care personnel handwash, skin antiseptic, and surgical hand scrub) and marketing a product in conformance with two or more produ t categories becomes difficult because there are different labeling requirements for each drug product category. Some comments requested FDA to combine the drug product category designations or to add a new multipurpose product category that allows the combining of labeling indications now included in several product categories. One comment specifically recommended that the agency consider changing product class designations and/or adding a new product class "Multi Purpose Skin Prep" or "Skin Prep," with the indications for use including those listed under § 333.85 (health-care personnel hand wash), § 333.87 (patient preoperative skin preparation), § 333.90 (skin antiseptic), and § 333.97 (surgical hand scrub).

Another comment stated that the word "skin" was superfluous because all OTC antiseptics are intended only for use on the skin; still another comment contended that the statement of identity "antiseptic" is preferable to "skin antiseptic" because these products are used on cuts, scratches, and mucous membranes as well as skin.

In response to the advance notice of proposed rulemaking and reopening of the administrative record for alcohol drug products for topical antimicrobial OTC use published in the **Federal Register** of May 21, 1982 (47 FR 22324), one comment objected to the statement of identity in proposed § 333.98(a) which read, "alcohol for topical antimicrobial use," (47 FR 22324 at 22332). The comment stated that this term would be confusing to the consumer and suggested the term "antiseptic for the skin."

The agency agrees that OTC topical antimicrobial drug products need not have multiple statements of identity. In reviewing the statements of identity recommended by the Antimicrobial I Panel (39 FR 33103), i.e., health-care personnel handwash, patient preoperative skin preparation, skin antiseptic, surgical hand scrub, and the statement of identity recommended by the Miscellaneous External Panel (47 FR 22324), i.e., alcohol for topical antimicrobial use, the agency has determined that the general term "antiseptic" broadly describes all proposed product categories and reflects the basic intended uses of these

products. The agency believes that the statement of identity of "multiple purpose skin prep" or "skin prep" recommended by one comment would not as clearly and succinctly describe the use of these products as the statement of identity "antiseptic." As discussed in section I.B., comment 5, the agency is also proposing an additional term "antiseptic handwash" as a statement of identity to describe products for home use.

As discussed in the first aid antiseptic segment of this rulemaking (56 FR 33644 at 33647), the term "skin" has been deleted from the previously proposed statement of identity "skin antiseptic." Although several comments felt that the word "skin" was superfluous, the agency has no objection to the statement "antiseptic for the skin" or "skin antiseptic" appearing elsewhere in the labeling of these products as additional information to the consumer or health-care professional, provided it does not appear in any portion of the labeling required by the monograph and does not detract from such required information. (See section I.I., comment 19.)

As stated in the first aid antiseptic segment of this rulemaking (56 FR 33644 at 33647), the agency believes that the term "antiseptic" is readily understood by consumers. The agency also finds this to be true for health professionals. The agency is therefore proposing the term "antiseptic" as the general statement of identity for all OTC topical antimicrobial ingredients included in this tentative final monograph. Further, FDA is also proposing that manufacturers may have an option to provide an alternate statement of identity describing only the specific intended use(s) of the product. Specifically, the agency is proposing that the statement of identity for antiseptic drug products in § 333.450(a) read as follows: "The labeling of a single-use product contains the established name of the drug, if any, and identifies the product as an 'antiseptic' and/or with the appropriate statement of identity described in §§ 333.455(a), 333.460(a), or 333.465(a). The labeling of a multiple-use product contains the established name of the drug, if any, and may use the single statement of identity 'antiseptic' and/or the appropriate statements of identity described in §§ 333.455(a), 333.460(a), and 333.465(a). When 'antiseptic' is used as the only statement of identity on a single-use or a multiple-use product, the intended use(s), such as patient preoperative skin preparation, is to be included under the indications. For multiple-use products, a statement of the intended use should also precede the specific directions for each use."

The agency believes that the proposed labeling for these multiple-use products is flexible and provides manufacturers with a number of options. However, the agency recognizes that some manufacturers may wish to label their antiseptic drug products with all of the allowable indications for a particular active ingredient and that this may give rise to difficulties in incorporating all of the information on a product's various uses in the limited space on an OTC label. The agency wishes to point out that some portions of the proposed indications are optional, i.e., the examples included in both the antiseptic and health-care personnel handwash indications, and need not be incorporated in the labeling at all. In addition, manufacturers are free to design ways of incorporating all the information on the various uses of their drug product through the use of flap labels, redesigned packages, or package inserts.

The agency is providing several examples of labeling for an antiseptic product containing povidone-iodine when labeled as a single-use or as a multiple-use product, as follows:

1. When labeled as a single-use product, i.e., patient preoperative skin preparation.

a. Established name: povidone-iodine.

b. Statement of identity (any of these is acceptable):

(1) "antiseptic";

(2) "patient preoperative skin preparation";

(3) "antiseptic/patient preoperative skin preparation."

c. Indications:

(1) When only "antiseptic" is used in the statement of identity:

"Patient preoperative skin preparation:

Helps to reduce bacteria that potentially can cause skin infection."

(2) When patient preoperative skin preparation is used as or included as part of the statement of identity: "Helps to reduce bacteria that potentially can cause skin infection."

d. Directions: (Insert directions in § 333.460(d).)

2. When labeled as a multiple-use product, i.e., patient preoperative skin preparation, antiseptic handwash or health-care personnel handwash, and surgical hand scrub.

a. Established name: povidone-iodine.

b. Statement of identity (any of these is acceptable):

(1) "antiseptic";

(2) "patient preoperative skin preparation, antiseptic handwash or health-care personnel handwash, and surgical hand scrub";

(3) "antiseptic/patient preoperative skin preparation, antiseptic handwash or health-care personnel handwash, and surgical hand scrub."

c. Indications: Irrespective of which statement of identity is used, the following is required: "Patient preoperative skin preparation: Helps to reduce bacteria that potentially can cause skin infection. Antiseptic handwash: For handwashing to reduce bacteria on the skin (which may be followed by one or more of the following: after changing diapers, after assisting ill persons, or before contact with a person under medical care or treatment). Health-care personnel handwash: Handwash to help reduce bacteria that potentially can cause disease or For handwashing to reduce bacteria on the skin (which may be followed by one or more of the following: after changing diapers, after assisting ill persons, or before contact with a person under medical care or treatment). Surgical hand scrub: Significantly reduces the number of micro-organisms on the hands and forearms prior to surgery or patient care."

d. Directions: The following is required: Patient preoperative skin preparation: (Insert directions in § 333.460(d).) Antiseptic handwash or health-care personnel handwash: (Insert directions in § 333.455(c).) Surgical handscrub: (Insert directions in § 333.465(c).)

4. One comment requested that scrubbing devices such as brushes or sponges that are impregnated with approved antimicrobial ingredients be included in the monograph. Another comment requested clarification of the agency's views on trays or kits that contain povidone-iodine and disposable instruments (scissors, forceps, and hemostats) packed in a sterile package, which are designed to reduce the incidence of cross-infection in hospitals.

This tentative final monograph does not provide for the use of devices such as brushes or sponges impregnated with antimicrobials, or of trays or kits that contain povidone-iodine and disposable instruments, because the monograph is intended to regulate only OTC drug active ingredients. Since these comments were submitted, the agency has established procedures (see 21 CFR part 3) describing how it determines which agency component has primary jurisdiction for the premarket review and regulation of products comprised of any combination of a drug and a device. In addition, interested parties are encouraged to read the following document (Ref. 1) for guidance: "Intercenter Agreement Between the

Center for Drug Evaluation and Research and the Center for Devices and Radiological Health." (See § 3.5 (21 CFR 3.5).) This agreement is on file in the Dockets Management Branch (address above)

(1) Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health in OTC Vol. 230001, Docket No. 75N–183H, Dockets Management Branch.

5. One comment expressed concern that the tentative final monograph failed to provide consumers with an antibacterial skin cleanser for home use. The comment noted that, in addition to professional health care personnel, many consumers have a need for cleansing products containing antibacterial agents for the purpose of promoting good individual and family hygiene. Uses for such products include the following: (1) To reduce bacteria on the hands and face to a greater extent than can be accomplished with ordinary soap, and to prevent accumulation of bacteria from potential sources of contamination. The following examples were cited: Cleansing oneself after changing a baby's diaper, or after assisting aged or ill members of the household with their toilet needs, and before preparing a family meal. (2) The added benefit of an antibacterial cleanser for the minute cuts and abrasions from shaving and other minor traumas. (3) The need for an antibacterial cleanser other than bar soap on local parts of the body such as the face because soap (alkali salts of fatty acids) can be irritating or too drying for some individuals' needs. The comment recommended a new product class under proposed § 333.90(a) (skin antiseptic) to be identified as "Antimicrobial (or Antibacterial) Personal Cleanser" with claims such as "decreases bacteria on the skin" and "contains an antibacterial agent." The comment also suggested that the 10-day maximum use limitation would not be appropriate for this product class, but use could be restricted to 5 or 10 times daily.

Another comment recommended that antimicrobial soaps be allowed to make claims relating to general health care and personal hygiene similar to the claims allowed for health-care personnel handwashes. The comment stated that an antimicrobial soap will reduce bacteria or the transfer of potentially pathogenic micro-organisms in the home and, therefore, serves as a preventive health care aid in controlling diseases.

A third comment requested the addition of a fourth indication for alcohol active ingredients in proposed § 333.98(b) to allow use as an antibacterial handwash to avoid cross-contamination from one individual to another. The comment argued that products containing alcohols are often used as handwashes by athletic trainers to help prevent the spread of skin infections from one individual to another in situations in which soap and water are not available, e.g., on the playing field.

A fourth comment asserted that numerous other meaningful and truthful indications can be used which enhance the safe and effective use of a health-care personnel handwash. For example, the terms "microbicidal cleanser" or "antiseptic germicidal skin cleanser" are appropriate and meaningful terminology describing this use indication.

The agency agrees that antibacterial or antiseptic personal cleanser products are practical for home use, to help prevent cross contamination from one person to another, especially after diaper changing and caring for invalids or ill family members. The agency also agrees with one comment that claims relating to general health-care and personal hygiene similar to the claims allowed for health-care personnel handwashes may be suitable because such claims explain the uses of these products in lay terms.

In the **Federal Register** of July 22, 1991 (56 FR 33644), the agency separated the first aid antiseptic uses of OTC topical antimicrobial drug products from the "non-first aid uses." In that document, the agency proposed that the following terms and categories be deleted: skin antiseptics, skin wound protectants, and skin wound cleansers; and the agency proposed that the appropriate labeling, instead, be included in a new category called "first aid antiseptics" (56 FR 33644 at 33649). Several uses proposed by one comment, i.e., "minute cuts and abrasions from shaving and other minor traumas," are considered as describing "first aid uses" and are adequately covered by the labeling provided for "first aid antiseptics" in proposed § 333.50(b) (56 FR 33677), which contains the following: "First aid to help" (select one of the following: "prevent," ("decrease" ("the risk of" or "the chance of")), ("reduce" ("the risk of" or "the chance of")), "guard against," or "protect against") (select one of the following: "infection," "bacterial contamination," or "skin infection") "in minor cuts, scrapes, and burns." The agency believes that the first aid indication is sufficiently broad to cover minute cuts and abrasions from shaving and that it is not necessary to include the words "other minor traumas" in the indications statement.

Beyond the first aid uses described in the first comment, the agency recognizes a need for an OTC "antiseptic handwash" product for repeated or daily use over an extended period of time for some of the other uses described by the comment. The agency agrees with the comments that health-care personnel handwashes are appropriate for such use because submitted data from effectiveness studies, for uses subject to this rulemaking, were derived from handwashing tests similar to or the same as tests described in the agency's previously proposed testing guidelines (see 43 FR 1210 at 1240), i.e., "Modified Cade Procedure," "Glove Juice Test," and "Test for Health-Care Personnel Handwash Effectiveness." The agency is proposing in this tentative final monograph in § 333.455(a) that a health-care personnel handwash can also bear a statement of identity of "antiseptic handwash." (See section I.B., comment 3.) For products labeled for multiple uses including both antiseptic handwash and first aid labeling claims, the general statement of identity would be "antiseptic" as described in section I.B., comment 3. The product would then need to incorporate the monograph labeling for both antiseptic handwash as well as first aid antiseptic.

The term "cleanser" included in claims requested by the comments is not appropriate in this rulemaking because it is considered to be a cosmetic claim in view of the fact that the Federal Food, Drug, and Cosmetic Act (the act) defines a cosmetic as "articles intended to be * * * applied to the human body * * * for cleansing * * *" (21 U.S.C. 321(i)(1)) and thus may be misleading to consumers. As discussed in section I.I., comment 19, the terms "microbicidal" and "germicidal" may appear in the labeling of OTC antiseptic drug products under certain conditions.

Accordingly, the agency is proposing as the indication for products bearing the statement of identity "antiseptic handwash" a general claim similar to one recommended by one of the comments, i.e., "for handwashing to decrease bacteria on the skin." The agency has determined that this claim may, at the manufacturer's option, be followed by one or more of the following examples: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment."

Descriptive statements such as "contains antibacterial ingredients" and "for the purpose of promoting good

individual and family hygiene" are considered to be examples of statements not significantly related to the safe and effective use of the product and thus are outside the scope of the rulemaking. Such statements may be included in the labeling of these OTC drug products subject to the statutory provisions against false or misleading labeling.

The agency has determined that the indication proposed for antiseptic handwash drug products is also appropriate for health-care personnel handwashes and is also proposing the following indication for health-care personnel handwashes. "For handwashing to decrease bacteria on the skin" (which may be followed by one or more of the following: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment.") In addition to the indication proposed above, the agency is proposing that health-care personnel handwashes may also bear the following indication: "Handwash to help reduce bacteria that potentially can cause disease." The agency is proposing the statement "recommended for repeated use" as an "other allowable indication" for antiseptic or health-care personnel handwash drug products (see below).

The agency sees no reason to continue to include "antimicrobial soap" as a separate product category. Soap is considered to be a dosage form, and specific dosage forms are not being included in the monograph unless there is a particular safety or efficacy reason for doing so. Antimicrobial ingredients may be formulated as soaps for some of the uses discussed in this document, e.g., handwash; however, the designation "antimicrobial soap" is no longer being proposed for inclusion in the monograph. In addition, the agency considers the other product categories that are being proposed to be more informative to the users of these products.

Based upon the comments, the agency is proposing labeling appropriate for professional or consumer uses as follows:

Section 333.455 Labeling of Antiseptic Handwash or Health-Care Personnel Handwash Drug Products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antiseptic," as stated above under § 333.450(a), and/or "antiseptic handwash," or "health-care personnel handwash."

(b) *Indications.* * * *

(1) *For products labeled as a health-care personnel handwash.* "Handwash to help reduce bacteria that potentially can cause disease" or "For handwashing to decrease bacteria on the skin" (which may be followed by one or more of the following: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment.")

(2) *For products labeled as an antiseptic handwash.* "For handwashing to decrease bacteria on the skin" (which may be followed by one or more of the following: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment.")

(3) *Other allowable indications for products labeled as either antiseptic or health-care personnel handwash.* The labeling of the product may also contain the following phrase: "Recommended for repeated use."

Other labeling claims requested by the comments for first aid antiseptics are not being included in the tentative final monograph. The agency believes that the general claim "for handwashing to decrease bacteria on the skin" encompasses the variety of uses for promoting good individual and family hygiene. The agency tentatively concludes that the labeling statements proposed above express the same concepts as the labeling suggested by the comments in language that can be more readily understood by the consumer.

C. Comments on Definitions

6. One comment objected to a portion of the definition for health-care personnel handwash in § 333.3(d) of the tentative final monograph that states that the antimicrobial agent is "broad-spectrum" and "if possible, persistent." The comment argued that, because these handwashes are used 50 to 100 times daily, persistence of effect is unnecessary. The comment also questioned the need for a broad-spectrum antimicrobial, stating that *Staphylococcus epidermidis* (*S. epidermidis*) generally is the only natural resident bacteria on the skin, and other transient micro-organisms are more likely to be removed mechanically by washing than by antimicrobial action. The comment suggested that the choice to use or not to use a broad-spectrum antimicrobial ingredient should be left to the manufacturer.

Another comment pointed out that the requirement for "broad spectrum" activity is inconsistently applied in the definitions for health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub (§ 333.3(d), (e), and (i), respectively) because "broad spectrum" activity is mandatory for the first two classes and only "desirable" for surgical hand scrubs. The comment cited comment 93 (43 FR 1210 at 1224) and the testing guidelines for safety and effectiveness of OTC topical antimicrobials (43 FR 1239) to show the agency's awareness of possible shifts in microbial flora due to a lack of broad spectrum activity. The comment urged that all three product classes include the requirement for each product to at least demonstrate in vitro "cidal" activity against gram-negative bacteria, fungi, and lipophilic and hydrophilic viruses in addition to the gram-positive activity.

In § 333.3(d) of the previous tentative final monograph, a health-care personnel handwash was defined as an "* * * antimicrobial-containing preparation designed for frequent use; it reduces the number of transient micro-organisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying, and it is broad-spectrum, fast acting, and, if possible, persistent." In the tentative final monograph, the agency agreed with the Panel that persistence, defined as prolonged activity, is a valuable attribute that assures antimicrobial activity during the interval between washings and is important to a safe and effective health-care personnel handwash (43 FR 1215). The Panel explained that a property such as persistence, which acts to prevent the growth or establishment of transient micro-organisms as part of the normal baseline or resident flora, would be an added benefit (39 FR 33103 at 33115). Although the Panel did not propose persistence as a mandatory requirement for a health-care personnel handwash, the agency is retaining the words "if possible, persistent" in the definition in this amended tentative final monograph because this is a desirable trait for these products.

Regarding the comment's objection to the broad-spectrum requirement, the Panel in its discussion of the normal skin flora stated that the predominant members of the normal flora are gram positive cocci and diptheroids and not *S. epidermidis*, as the comment indicates. The Panel stated further that a small number of gram negative species, such as coliforms and related micro-organisms, as well as higher forms such as yeast may also be residents of the skin of healthy individuals (39 FR 33103 at 33107). In its discussion of health-care personnel handwash drug products, the Panel acknowledged that, in all likelihood, the specified effect of these products (i.e., removal of transient micro-organisms) can be achieved with a well formulated

nonantimicrobial soap or detergent product. However, the Panel concluded that transient micro-organisms may become part of the established "resident" flora with time, and stated that in a health-care situation, the fast, effective removal of transient micro-organisms is a requirement because they may be pathogenic (39 FR 33103 at 33115). The Panel recommended that health-care personnel handwash drug products containing an antimicrobial ingredient should be broad spectrum. The Panel defined "broad spectrum" in reference to microbiological activity as meaning the antimicrobial has activity against more than one type of micro-organism, that is, activity against gram positive and gram negative bacteria, fungi, and viruses (39 FR 33115). Because transient micro-organisms present on the skin may include widely diverse species, resulting from contact with contaminated persons and materials, the agency concludes that a greater reduction of transient micro-organisms on the skin can be achieved if the antimicrobial containing drug product used as a health-care personnel handwash provides broad spectrum activity.

In addition, because the principal intended use of these professional use products is the prevention of nosocomial (hospital acquired) infections, the agency believes that these drug products should have demonstrable antimicrobial activity against a microbial spectrum that includes the micro-organisms associated with these infections. As discussed in section I.N., comment 28, the agency is proposing, in § 333.470(a)(1)(ii) of the testing requirements, a list of micro-organisms that reflects a spectrum of antimicrobial activity pertinent to the intended use of these drug products and against which the products must be tested. The agency is proposing the following definition of broad spectrum activity in § 333.403(b) of this amended tentative final monograph: "*Broad spectrum activity.* A properly formulated drug product, containing an ingredient included in the monograph, that possesses in vitro activity against the micro-organisms listed in § 333.470(a)(1)(ii), as demonstrated by in vitro minimum inhibitory concentration determinations conducted according to methodology in § 333.470(a)(1)(ii)." This methodology has been developed by the National Committee for Clinical Standards (NCCLS) (Ref. 1). Although micro-organisms in addition to those listed may also be used for testing, the agency will use the test micro-organisms identified in § 333.470(a)(1)(ii) for any necessary compliance testing.

The agency wants to emphasize that in this amended tentative final monograph the broad-spectrum criterion applies to final-formulated drug products used as an antiseptic handwash or health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub. Although the Category I active ingredients currently included in this amended tentative final monograph are broad spectrum independent of formulation, some Category III antiseptic ingredients have limited spectra (activity against only gram positive bacteria; for example, chloroxylenol (see section I.G., comment 12) and triclosan (see section I.L., comment 23)), but when properly formulated in a final product the spectrum can be broadened to include additional activity against the test micro-organisms, thereby possibly enabling these ingredients to become Category I. Although the agency agrees with the first comment that the manufacturer may use or not use a broad-spectrum ingredient in a particular health-care antiseptic drug product, the finished product must demonstrate in vitro activity against the specific micro-organisms listed in proposed § 333.470(a)(1)(ii).

In response to the second comment, that broad spectrum was inconsistently applied in the definitions of the three product classes, the agency has reevaluated the issue and believes that all product classes should be broad spectrum. As stated in the tentative final monograph (43 FR 1210 at 1212), maintaining the balance among species of micro-organisms constituting the normal skin flora is more likely to be threatened by use of antimicrobial products with a limited spectrum. Also much of the data concerning the spread of infections in hospitals indicates that the use of an antimicrobial with broad spectrum activity would help prevent this (see section I.D., comment 9). Based on the reasons mentioned above, the agency is proposing to include "broad spectrum" in the definitions of the three product classes included in this tentative final monograph.

Reference

(1) National Committee for Clinical Laboratory Standards, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—2d ed.; Approved Standard," NCCLS Document M7-A2, 10:8, 1990.

D. Comments on Labeling

7. Several comments contended that FDA does not have the authority to restrict OTC labeling claims to exact wording, to the exclusion of what the comments described as other "equally truthful claims for the products." One comment pointed out that numerous other meaningful and truthful statements will provide useful information and will enhance the safe and effective use of these products. Several comments maintained that manufacturers have a constitutional right to use any truthful, nonmisleading labeling under the first amendment. To support their position, the comments cited *Bigelow* v. *Virginia*, 421 U.S. 809 (1975); *Virginia State Board of Pharmacy* v. *Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976); *Linmark Associates, Inc.* v. *Willingboro*, 431 U.S. 85 (1977); *Bates* v. *State Bar of Arizona*, 433 U.S. 350 (1977); *Federal Trade Commission* v. *Beneficial Corp.*, 542 F.2d 611, 97 S. Ct. 1679 (1977); and *Warner-Lambert Co.* v. *Federal Trade Commission*, 562 F.2d 749 at 768 (D.C. Cir. 1977).

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g).

In the previous tentative final monograph, supplemental language relating to indications had been proposed and captioned as *Other Allowable Statements* in §§ 333.85, 333.87 and 333.97. Under FDA's revised labeling policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful

and nonmisleading language that would be allowed elsewhere in the labeling. In accordance with the revised labeling policy, such statements would not be included in a final monograph.

In preparing this amended tentative final monograph, the agency has reevaluated these "other allowable statements" to determine whether they should be incorporated, wherever possible, as part of the indications developed under the monograph.

The agency has reviewed the "*Other Allowable Statements*" proposed in the previous tentative final monograph in § 333.85 for health-care personnel handwash, in § 333.87 for patient preoperative skin preparation, and in § 333.97 for surgical hand scrub. The statement "recommended for repeated use" proposed for a health-care personnel handwash has been included in this amended tentative final monograph as an "other allowable indication" in proposed § 333.455 for antiseptic handwash or health-care personnel handwash drug products. (See section I.B., comment 5.)

The terms "broad spectrum" and "fast-acting" (if applicable) were proposed as "*Other Allowable Statements*" for all three of these product classes in the previous tentative final monograph. As discussed in section I.C., comment 6, the agency is proposing to include "broad spectrum" in the definition of the three product classes included in this amended tentative final monograph. Although the term "broad spectrum" is included in the definitions of these product classes, the agency does not see a need to include this information in the "indications" for these products. Likewise, the term "fast-acting" is included in the definitions of these product classes, but the agency does not see a need to include this information in the indications for these products. This type of information may appear elsewhere in the labeling of these products as additional information to the health-care professional, provided it does not appear in any portion of the labeling required by the monograph and does not detract from such required information. Other previously proposed "*Other Allowable Statements*," i.e., "contains antibacterial ingredient(s)," "contains antimicrobial ingredient(s)," and "nonirritating," are not related in a significant way to the safe and effective use of these products. The agency does not believe that statements such as "contains antibacterial ingredient(s)" or "contains antimicrobial ingredient(s)" are necessary on products intended primarily for health professionals, but has no objection to such statements appearing in the labeling as other information not intertwined with any portion of the labeling required by the monograph. Likewise, the term "nonirritating" may appear as additional information to the health-care professional, provided it does not appear in any portion of the labeling required by the monograph and does not detract from such required information. However, such statements are subject to the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such statements will be evaluated on a product-by-product basis, under the provisions of section 502 of the act relating to labeling that is false or misleading.

8. Several comments requested that certain warnings required in the labeling of OTC drug products marketed for the general public should not be required on such products distributed only to health professionals and labeled primarily for use in health-care facilities as in proposed § 333.99 "Professional labeling" (43 FR 1210 at 1248 and 1249). Examples cited were the cautionary statements for "skin antiseptic" and "skin wound protectant" in proposed §§ 333.90(c)(3) and 333.93(c)(3) "Do not use this product for more than 10 days. If the infection (condition) worsens or persists, see your physician," and for "skin wound protectant" in proposed § 333.93(c)(7) "Do not use on chronic skin conditions such as leg ulcers, diaper rash, or hand eczema." The comments stated that the professional use of these products sometimes differs from consumer use and that products which are marketed only to health-care institutions and are dispensed and administered by professionals should only contain warnings that apply to professional use. One comment concluded that requiring professional labeling to contain a caution such as in proposed § 333.93(c)(7) could possibly subject the health-care facility and the physician to unwarranted product liability claims, although the particular use of the product under medical supervision is entirely justified and necessary for proper treatment of the patient. One of the comments stated that flexibility should be provided so that manufacturers can utilize only those warnings that are appropriate for professional personnel when packages are restricted to health-care facilities or where a topical antimicrobial product is used as part of a course of treatment selected by the clinician.

In the **Federal Register** of November 12, 1973 (38 FR 31260), the agency published the tentative final monograph for OTC antacid drug products, in which the concept of ethical labeling for OTC drug products was first discussed in comment 56 at 38 FR 31264. There, the agency stated that the warning statements appearing on OTC drug products should be included in ethical (professional) labeling.

Subsequently, in the previous tentative final monograph for OTC topical antimicrobial drug products, published in the **Federal Register** of January 6, 1978 (43 FR 1210), the agency proposed § 333.99 ("Professional labeling") which stated that the labeling of products (covered by the monograph) that is provided only to health professionals and the labeling for those products primarily used in health-care facilities shall include all of the warnings required in each subsection of the monograph, e.g., those in § 333.90 for "skin antiseptic" or § 333.93 for "skin wound protectant."

As described in the first aid antiseptic segment of the tentative final monograph for OTC antimicrobial drug products, published in the **Federal Register** of July 22, 1991 (56 FR 33644), the agency has proposed deletion of the categories cited by the comments, i.e., "skin antiseptic" and "skin wound protectant," as separate drug categories and included them in a single drug product category identified as "first aid antiseptic." The cautionary statements referred to by the comments are addressed in that document.

In this document, the agency is addressing the uses other than first-aid, i.e., health-care antiseptic uses, of topical antimicrobial drug products. These products may contain the same antiseptic active ingredient(s) as the first aid antiseptic drug products, but they are labeled and marketed for different uses. The cautionary statements previously proposed in §§ 333.90(c)(3) and 333.93(c)(3) addressed short-term first aid uses of products primarily proposed as "consumer products." These products were not principally intended to be marketed for hospital or professional use. Therefore, the agency agrees with the comments that such cautionary statements do not apply to professional use of antiseptic drug products and need not appear in the labeling of antiseptic products marketed as antiseptic handwashes or health-care personnel handwashes, patient preoperative skin preparations, and surgical hand scrubs. Likewise the agency believes that health-care antiseptic drug products, marketed principally to health-care professionals, do not need to bear a cautionary statement not to use the product on chronic skin conditions such as leg ulcers, diaper rash, or hand eczema. As

the comment pointed out, professional use of these products is different than consumer use and, in some instances, use of the product on the above-mentioned skin conditions under medical supervision may be justified and necessary for proper treatment of the patient. Therefore, this cautionary statement is not being included in this tentative final monograph.

This tentative final monograph addresses specifically the use of these topical antiseptic drug products by health-care professionals and in health-care facilities. The labeling proposed for those products in this document represents that labeling which the agency believes health-care professionals need to properly use these products. Therefore, the agency believes that the warnings proposed in § 333.450(c) of this tentative final monograph should appear in the labeling of these products that are directed to health-care professionals and health-care facilities, even if the product is marketed principally to these sources only. However, the agency believes that one of these warnings can be modified if the product is labeled "For Hospital and Professional Use Only." In such cases, the second sentence of the warning proposed in § 333.450(c)(3), regarding consulting a doctor, can be deleted. This concept is being included in this tentative final monograph. (See § 333.450(d).)

In responding to the comments regarding the warnings in the "Professional labeling" section (§ 333.99) of the previous tentative final monograph, the agency has determined that these warnings are no longer necessary. Accordingly, § 333.99 is not being included in this amended tentative final monograph. (See section I.D., comment 9 for discussion of § 333.99(a), and section I.J., comment 21 for discussion of § 333.99(b). Also, see section II.B., paragraph 14 in the first aid antiseptic segment of this tentative final monograph (56 FR 33644 at 33675) for discussion of § 333.99(c).)

9. Several comments made recommendations regarding the requirement that professional labeling for all classes of OTC topical antimicrobial drug products must contain the caution statement in proposed § 333.99(a), "Caution: Overuse of this and other antimicrobial products may result in an overgrowth of gram-negative micro-organisms, particularly *Pseudomonas*." Some of the comments stated that this caution statement should be required only for antimicrobials where there is valid scientific evidence to show that such caution is appropriate, for example, quaternary ammonium compounds and triclosan, which have been associated with the overgrowth of gram-negative micro-organisms, specifically *Pseudomonas*. Three comments contended that reports of contamination of benzalkonium chloride solutions with *Pseudomonas* and *Enterobacteria* species were basically the result of misuse, improper storage and dilution, poor technique, and contamination with neutralizing chemicals. One comment recommended that the proposed caution statement in § 333.99(a) should be changed to read: "Improper use or overuse * * *." and cited the discussion of the proposed warning for quaternary ammonium compounds by the agency at 43 FR 1237 where the phrase "misuse or overuse" was included. Another comment objected to the caution, arguing that it is based on theoretical considerations only and there is no published clinical evidence implicating quaternary ammonium compounds. Still another comment stated that its quaternary ammonium compound product passed the commonly used test for *Pseudomonas* activity.

In defense of triclosan's implication in *Pseudomonas* overgrowth, one comment argued that overgrowth was just an unproven hypothesis and submitted the "Summary for Basis of Approval" from an approved new drug application (NDA) for chlorhexidine gluconate (Ref. 1) which included data on a skin flora study that indicated an increasing, continuous gram-negative growth only in the axillary area over a 6-month period, even though chlorhexidine is active against gram-negative micro-organisms. The comment referred to FDA's Division of Anti-Infective Drug Products as having recognized that gram-negative overgrowth can be adequately controlled by restricting use to indications provided in the labeling of a product.

Several comments pointed out that data on povidone-iodine have proven broad spectrum effectiveness, referring to the Centers for Disease Control and Prevention's (CDC) recommendation (Ref. 2) for using this ingredient for skin preparation before intravenous catheter insertion and other procedures to reduce infection. The comments also noted that in a study by Houang et al. (Ref. 3), in which 20 transfers of 7 gram-negative micro-organisms (including *Pseudomonas aeruginosa* (*P. aeruginosa*)) were made, the minimum inhibitory concentration did not change, supporting the fact that repeated use of povidone-iodine would not result in resistant micro-organisms. For these reasons, these comments recommended that § 333.99(a) should be revised to exclude povidone-iodine.

After a thorough review and evaluation of the available data, the agency concludes that the professional labeling caution that overuse of an antimicrobial drug product may cause an overgrowth of gram-negative micro-organisms is not necessary. In the previous tentative final monograph (43 FR 1210 at 1212), the agency stated its awareness of the theory that gram-negative bacteria will replace gram-positive bacteria that are reduced in number or eliminated by use of antimicrobials and encouraged research to test the validity of the theory. The agency also recalled the Panel's highlighting the need for research on microbial ecology of the skin and its concern about the effect of overuse of antimicrobial drug products, especially products with a limited spectrum, in hospitals and other closed populations. Therefore, the agency proposed the professional labeling caution in § 333.99(a) "for certain antimicrobial ingredients approved for OTC drug use * * * used in health-care facilities" (43 FR 1213). However, the agency concluded that the limited consumer use of these products in the population at large did not constitute a risk that would warrant such a label warning. Although benzalkonium chloride has been frequently implicated in *Pseudomonas* hospital infections, the agency's review of numerous reports and studies on quaternary ammonium compounds and other antimicrobials (Refs. 4 through 10) indicates that specific causes for contamination, such as lack of aseptic technique when applying intravenous infusions and sterilization failure of the items used (bottles, tubing, distilled water used in diluting benzalkonium chloride), were the problem and not overuse of benzalkonium chloride. The agency discussed this problem in the previous tentative final monograph and stated that it appears that practices in the health-care facility environments where quaternary ammonium compounds are commonly used often fall short of the minimum necessary to prevent outbreaks of infection. (See comment 51 43 FR 1210 at 1216.) Benzalkonium chloride is more prone to become contaminated for several reasons that were brought out in the studies: (1) *Pseudomonas* species are among the bacteria most resistant to surface-active agents like quaternary ammonium compounds. (2) The usual quaternary ammonium compound concentration appears to be ineffective against some species, such as *Pseudomonas cepacia*,

an organism which has been reported to have been associated with hospital infections. One study showed that this organism survived 14 years in a salt solution preserved with 0.05 percent benzalkonium chloride. (3) Organic materials (gauze, cotton, cork in stoppers, soaps), inorganic matter, protein, and anionic substances inactivate quaternary ammonium compounds. (4) Hospital personnel are unfamiliar with these problems and with procedures for using quaternary ammonium compounds safely and effectively. Based on these reports, the agency agrees with the comments that "improper" use, not "overuse," is the cause of benzalkonium chloride being implicated in *Pseudomonas* contamination and that there is a lack of data demonstrating "overuse" to be the cause.

The agency also agrees with the comment which stated that it was an unproven hypothesis that overuse of an antiseptic causes *Pseudomonas* overgrowth. The "Summary for Basis of Approval" from an approved NDA for chlorhexidine gluconate (Ref. 1) cites a skin flora study that indicated that the axilla was an area where gram-negative micro-organisms continued to be isolated even though chlorhexidine gluconate has shown gram-negative effectiveness. The comment cited FDA's Division of Anti-Infective Drug Products' recognition that for health-care uses, such as surgical scrub and health-care personnel handwash, there would be no problem with *Pseudomonas* overgrowth because the hands are an area of the body not likely to support the growth of *Pseudomonas* because of the lack of moisture. In defending triclosan, the comment contended that this ingredient is bacteriostatic and does not eliminate all gram-positive bacteria; therefore, it would not predispose for gram-negative overgrowth. Triclosan has been implicated in *Pseudomonas* contamination because it is primarily effective against gram-positive bacteria, has limited in vitro and in vivo activity against gram-negative bacteria, and no activity against *Pseudomonas* (43 FR 1210 at 1232). One report showed that triclosan was effective against some gram-negative micro-organisms, but not effective against *Serratia* and *Pseudomonas* (Ref. 11). *Pseudomonas* and *Serratia* resistance caused the contamination, not overuse of the antiseptic.

The agency agrees with the comments that quaternary ammonium compounds and triclosan have been implicated in *Pseudomonas* hospital infections more frequently than povidone-iodine, but studies indicate that 'overuse' of these or any antimicrobial has not been the cause. *Pseudomonas* species may become dominant because of inherent resistant factors which enable them to survive the effects of many antibiotics and antiseptics (Refs. 12, 13, and 14). In addition, this genus is ubiquitous, found in both soil and water, and can multiply in almost any moist environment with even a trace of organic material (Ref. 15).

The agency believes that the data and reports have not provided specific evidence that repeated use of health-care antiseptics, including benzalkonium chloride and triclosan, have brought about overgrowth of gram-negative bacteria, particularly *Pseudomonas*. The agency agrees with the comments that improper use, failure of hospital personnel to use according to labeling indications, nonaseptic technique in diluting and handling, and lack of good quality control to ensure sterility of items in contact with antiseptics, such as sterile distilled water, hosing, and receptacles, are responsible.

The study by Houang et al. (Ref. 3) shows that repeated in vitro exposure of seven gram-negative micro-organisms, including *P. aeruginosa*, in povidone-iodine dilutions did not result in the development of resistance. The agency notes that CDC previously recommended povidone-iodine for use in intravenous catheter and other procedures (Ref. 2). However, there has been one report from CDC (Ref. 16) which described *Pseudomonas* hospital infections caused by intrinsically contaminated povidone-iodine (contaminated during manufacture, indicating failure of control of microbiological contamination). Compliance with the agency's regulations governing current good manufacturing practice for finished pharmaceuticals (21 CFR part 211) should prevent intrinsic contamination.

Accordingly, the agency concludes that a cautionary statement against overuse is not needed in the professional labeling of health-care antiseptic drug products. Therefore, the previously proposed caution in § 333.99(a) is not being included in this tentative final monograph. If new information indicates a need for a cautionary statement, the agency will consider appropriate action at that time.

References

(1) "Summary for Basis of Approval, Chlorhexidine Gluconate," NDA 17-768, Comment No. SUP022, Docket No. 75N-0183, Dockets Management Branch.

(2) "Recommendations for the Insertion and Maintenance of Plastic Intravenous Catheters," Paper for Training Purpose, Hospital Infections and Microbiological Control Sections, Bacterial Diseases Branch, Epidemiology Program, Centers for Disease Control, 1972.

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E. Comment on Alcohol

10. One comment submitted data on the safety and effectiveness of 62

percent alcohol formulated in an emolliented vehicle and dispensed as a foam (Ref. 1) and requested that alcohol be included in the topical antimicrobial monograph as a surgical hand scrub, health-care personnel handwash, and hand degermer.

Data on the safety and effectiveness of alcohol formulated in an emolliented vehicle for use as a surgical hand scrub, health-care personnel handwash, and hand degermer were submitted to the Miscellaneous External Panel (Refs. 2 and 3). However, the data were not reviewed or categorized for these uses during that rulemaking. In reviewing alcohol for short-term uses, that Panel stated, "ethyl alcohol acts relatively quickly to decrease the number of micro-organisms on the skin surface. Each minute that scrubbed hands and arms were immersed in approximately 77 percent ethyl alcohol by volume was found to be equivalent to 6.5 minutes of scrubbing in water; if the skin was scrubbed with the alcohol, the rate was further increased" (47 FR 22324 at 22328). The Panel found ethyl alcohol safe and effective for use as a topical antimicrobial preparation in concentrations of 60 to 95 percent by volume in an aqueous solution. The following indications were proposed:

(1) "For first aid use to decrease germs in minor cuts and scrapes."

(2) "To decrease germs on the skin prior to removing a splinter or other foreign object."

(3) "For preparation of the skin prior to an injection." (See the advance notice of proposed rulemaking for OTC alcohol drug products for topical antimicrobial use, in the Federal Register of May 21, 1982, 47 FR 22324.)

The submissions (Refs. 1 and 2) included effectiveness data and labeling for a currently marketed product containing 62 percent ethyl alcohol formulated in an emolliented vehicle and dispensed as a foam used "* * * to degerm hands * * *." The agency has reviewed these data, derived from effectiveness testing as a surgical hand scrub (glove juice test) and health-care personnel handwash, and finds that they meet the procedures in the testing guidelines in the previous tentative final monograph (43 FR 1210 at 1242). Statistical analyses showed microbial reduction to be highly significant. A glove juice test showed that alcohol foam reduced the baseline number of bacteria present in normal skin flora, after first use, by 1.67 logs, and, after continued use for 5 days, by 2.36 logs. The reduction of the baseline number of bacteria was maintained for up to 6 hours under surgical gloves. A health-care personnel handwash effectiveness test showed microbial reduction on test subjects' hands, artificially contaminated with *Serratia marcescens* (*S. marcescens*). Microbial reduction averaged 3.3 logs after 5 treatments and 3.63 logs after 25 treatments. In vitro data, derived from studies using *S. marcescens* as the test bacteria, showed that alcohol properly formulated in an emolliented vehicle and dispensed as a foam, significantly reduced the number of test bacteria, in 10 percent serum, within 15 seconds.

Based on these data and the conclusions of the Miscellaneous External Panel (47 FR 22324), the agency concludes that alcohol, when properly formulated, is effective for use as a surgical hand scrub and antiseptic handwash or health-care personnel handwash. Because it is well established that alcohol alone does not provide persistence, the agency notes that a preservative agent in the vehicle provided the persistent effect to maintain reduction in the baseline number of bacteria for 6 hours as required to demonstrate efficacy as a surgical hand scrub drug product.

The agency is including alcohol in proposed § 333.410(a) (antiseptic handwash or health-care personnel handwash), § 333.412(a) (patient preoperative skin preparation), and § 333.414(a) (surgical hand scrub), as follows: "Alcohol 60 to 95 percent by volume in an aqueous solution denatured according to Bureau of Alcohol, Tobacco and Firearms regulations in 27 CFR part 20." Further, the agency finds the Miscellaneous External Panel's proposed Category I indication for OTC alcohol drug products, i.e., "for preparation of the skin prior to an injection" to be an appropriate indication for patient preoperative skin preparation drug products. Based on that Panel's recommendations, the agency is including this indication as an additional claim for alcohol drug products in § 333.460(b)(2) of the proposed monograph. In addition, based on that Panel's similar recommendations for isopropyl alcohol (47 FR 22324 at 22329 and 22332), the agency is proposing this indication for OTC isopropyl alcohol drug products in § 333.460(b)(3). As discussed in section I.N., comment 28, the agency is proposing new effectiveness criteria for drug products labeled for this use.

The monograph will also state that an alcohol drug product must be properly formulated, such as the product in an emolliented vehicle dispensed as a foam discussed above, to meet the test requirements in § 333.470. This means that alcohol when intended for certain uses must be able to demonstrate effectiveness by certain tests proposed in this tentative final monograph, as follows: (1) Antiseptic or health-care personnel handwash—§ 333.470(b)(2), (2) patient preoperative skin preparation—§ 333.470(b) (3), and (3) surgical hand scrub—§ 333.470(b)(1). As discussed in section I.B., comment 5, the term "antiseptic handwash" in lieu of "hand degermer" is being proposed in the monograph as the statement of identity for this type of product.

The labeling for the alcohol product (Ref. 1) provides directions for use without water rinsing, where water is not readily available, as follows: "A 'palmful' (5 grams) is dispensed in one hand. It is spread on both hands and rubbed into the skin until dry (approximately 1 to 2 minutes). A smaller amount (2.5 grams) is then dispensed into one hand, spread over both hands to wrist, and rubbed into the skin until dry (approximately 30 seconds)." The agency concurs with these directions and is incorporating them into its proposed directions for use for OTC topical antiseptic drug products, including alcohol, formulated for use without water in this tentative final monograph. See proposed § 333.455(c) and § 333.465(c).

References

(1) Unpublished studies on emolliented alcohol foam (62 percent alcohol), Comments No. C105, C144, and CR7, Docket No. 75N-0183, Dockets Management Branch.

(a) Microbiological evaluation of "Alcare Hand Degermer" on personnel in a newborn intensive care unit, May 12, 1977.

(b) Results of a study of efficacy against experimental contamination of human skin, June 20, 1978.

(c) Efficacy study with Vestal Foam results of a glove fluid study, January 27, 1975.

(d) *Serratia marcescens* efficacy data for Alcare, February 20, 1978.

(e) Amended labeling for Alcare Foamed Alcohol, August 19, 1982.

(2) OTC Vol. 160377.

(3) OTC Vol. 160382.

F. Comments on Chlorhexidine Gluconate

11. Several comments requested that the agency include chlorhexidine gluconate as a Category I ingredient in any amended tentative final monograph. The comments submitted references and data to establish general recognition of safety and effectiveness (Ref. 1), and stated that chlorhexidine gluconate solution is recognized in the "British Pharmacopeia" (Ref. 2) and is formulated in a wide range of products that have been successfully marketed to a material extent and for a material length of time in other countries. The comments asserted that when

formulated in compliance with FDA's current good manufacturing practice regulations (21 CFR part 211), chlorhexidine products are safe and effective for use as skin wound cleansers, skin wound protectants, patient preoperative skin preparations, skin antiseptics, surgical hand scrubs, and health-care personnel handwashes.

A reply comment argued that chlorhexidine gluconate, currently marketed in the United States under approved new drug applications (NDA's), is not eligible for an OTC drug monograph because the ingredient has not been marketed within this country to a material extent and for a material length of time. The comment added that variations in final formulations may alter the safety and effectiveness of the ingredient. The comment submitted data (Ref. 3) to support this viewpoint and requested that chlorhexidine gluconate be classified in Category II.

In the previous tentative final monograph (43 FR 1210), chlorhexidine gluconate (4 percent solution) was neither addressed nor categorized as Category I, II, or III. However, subsequent to the tentative final monograph, the agency granted a petition (Ref. 4) and in the **Federal Register** of March 9, 1979, reopened the administrative record to allow interested persons an opportunity to submit data and information (44 FR 13041). The comments (Ref. 1) and reply comment (Ref. 2) were submitted in response to that notice. However, since that time a majority of the comments on chlorhexidine submitted in response to the notice have been withdrawn (Ref. 5). While the withdrawn comments remain on public display as part of the administrative record, they are no longer being considered in this rulemaking.

The agency has reviewed the marketing history of chlorhexidine gluconate and finds that although it has been marketed for professional or hospital use under NDA's, insufficient data remain in the public administrative record for this rulemaking to support general recognition of safety and effectiveness for OTC use. Accordingly, chlorhexidine gluconate 4 percent aqueous solution as a health-care antiseptic is a new drug and is not included in this tentative final monograph.

References

(1) Comments No. C110, C116, C120, C130, C131, C136, C137, EXT18, RC2, RC5, CP3, LET12, LET14, LET16, SUP30, SUP33, SUP36, and SUP40, Docket No. 75N–0183, Dockets Management Branch.

(2) "British Pharmacopeia," Vol. I, Her Majesty's Stationery Office, London, pp. 100–101, 1980.

(3) Comments No. RC1 and RC4, Docket No. 75N–0183, Dockets Management Branch.

(4) Comment No. CP3, Docket No. 75N–0183, Dockets Management Branch.

(5) Comments No. WDL3, WDL4, and WDL5, Docket No. 75N–0183, Dockets Management Branch.

G. Comments on Chloroxylenol

12. A number of comments disagreed with the agency's Category III classification of chloroxylenol in the tentative final monograph. They argued that a reevaluation of the data previously submitted to the agency along with new data that have been submitted (Refs. 1 through 16) would provide adequate justification for classifying chloroxylenol in Category I for safety and effectiveness for use in antimicrobial soaps, health-care personnel handwashes, patient preoperative skin preparations, skin antiseptics, skin wound cleansers, skin wound protectants, and surgical hand scrubs. Several comments pointed out that the Antimicrobial II Panel unanimously concluded that chloroxylenol is generally recognized as safe for topical use in athlete's foot and jock-itch preparations.

Based upon the submitted data (Refs. 1 through 16) and other information reviewed by the Antimicrobial Panels, the agency concluded in the amended tentative final monograph for OTC first aid antiseptic drug products that chloroxylenol (0.24 percent to 3.75 percent) was safe but not effective for short-term use as an OTC topical first aid antiseptic (54 FR 33644 at 33658). These data (Refs. 1 through 16) and new data submitted under the agency's "feedback" procedures (Refs. 17 through 30) are insufficient to support a Category I classification of the safety and effectiveness of the ingredient for other long-term uses, e.g., antiseptic handwash or health-care personnel handwash and surgical hand scrub. The agency concludes that chloroxylenol remains classified in Category III as an active ingredient for these uses. However, the ingredient would be considered safe for short-term use as a patient preoperative skin preparation but remains in Category III due to a lack of effectiveness data for this use.

In the previous tentative final monograph (43 FR 1210 at 1222 and 1238), the agency stated that the data were insufficient to reclassify chloroxylenol into Category I, and the ingredient remained in Category III for safety and effectiveness. Indicating concern about the absorption of topically applied antimicrobial drug products used repeatedly by consumers over a number of years, the agency stated the following regarding the safety of the ingredient:

> Only the most superficial toxicity data in animals were submitted to and reviewed by the Panel. The Commissioner concurs with the Panel that toxicity in rodent and nonrodent species, substantivity, blood levels, distribution and metabolism, as well as any subsequent systemic absorption studies must be characterized * * *. The degree of absorption of PCMX following topical administration has not been established. The target organ for PCMX toxicity in animals also remains unidentified and should be shown in a long-term animal toxicity study.

While safety data (Refs. 1, 2, 6, and 7) are sufficient to establish safety for short-term use such as for a patient preoperative skin preparation drug product, these data do not resolve concerns about long-term chronic toxicity. Conclusions on these data, which were also reviewed by the Advisory Review Panel on OTC Antimicrobial II Drug Products (Antimicrobial II Panel) in conjunction with its review of OTC topical antifungal drug products, were published in the **Federal Register** of March 23, 1982 (47 FR 12480). That Panel, which evaluated the safety of the ingredient for use in OTC topical antifungal drug products, categorized chloroxylenol (0.5 to 3.75 percent) as safe (Category I) for short-term use (up to 13 weeks) and advised, "* * * relatively low doses of chloroxylenol can be systemically tolerated, at least over a 13-week period. The Panel is concerned about the effect of chronic administration on the liver, but does not consider that topical application of chloroxylenol to small areas of the skin over short periods of time would result in liver damage." (47 FR 12480 at 12534). The agency subsequently agreed with the Panel's conclusions concerning the safety of using the ingredient in OTC topical antifungal drug products for the treatment of athlete's foot, jock itch, and ringworm (maximum treatment duration 4 weeks) in its tentative final monograph for these OTC drug products, published in the **Federal Register** of December 12, 1989 (54 FR 51136 at 51139). The agency subsequently finalized these conclusions in the final rule for OTC topical antifungal drug products published in the **Federal Register** of September 23, 1993 (58 FR 49890).

Regarding long-term chronic toxicity, data and information provided by one manufacturer included final reports of completed studies and interim reports

of incomplete studies (Ref. 2). The information also contained a protocol of a planned preclinical study (projected starting and completion dates for experiments) which identified a 2-year rat feeding study. Because this study might resolve concerns about long-term chronic toxicity, the agency requested the raw data (Ref. 31); however, the manufacturer declined to submit the data, explaining that it is no longer interested in marketing chloroxylenol, that its study had not been completed, and that the study was conducted prior to establishment of the Good Laboratory Practices regulations (Ref. 32).

In response to the agency's determination that data from a 2-year rat feeding study were essential (Ref. 33), another manufacturer submitted additional information along with copies of already available safety data (Ref. 34). The manufacturer explained that it believes that long-term safety data, i.e., 2-year oral feeding study, while not currently available, may not be a necessity. Citing statements made by the Panel, that its recommended guidelines for the safety testing of these drug products were developed primarily for antimicrobial agents applied to the entire body surface and that appropriate tests should be chosen to reflect the intended use of the antimicrobial drug product (39 FR 33103 at 33135), the manufacturer contended that the guidelines were developed to address the most extreme exposure to an antimicrobial ingredient rather than to describe the minimal requirements for safety data that the Panel would find acceptable. Noting the contrast between the use of surgical hand scrub drug products (products used by adults in a limited area of the body for a specified time span) with lifetime application to the entire body in bar soaps, the manufacturer contended that while the use of a surgical hand scrub is considered chronic use, the exposure to the antimicrobial ingredient during such use is limited to the hand and half the distance to the elbow. The manufacturer further suggested that one might simply regard the use of health-care antiseptic ingredients in handwashes and surgical scrubs as repeated daily use in a limited area of the body.

The manufacturer contended that data from a 2-year feeding study would not contribute any information on the long-term safety of chloroxylenol that is not already available from subchronic studies (Ref. 35). In support of its contention, the manufacturer submitted data from subchronic animal toxicity and human bathing studies (Ref. 18) previously submitted in response to the tentative final monograph for OTC topical antimicrobial drug products and to the Antimicrobial II Panel. The data also included computer simulation models (Ref. 36) of plasma levels of chloroxylenol that might occur after dermal applications of varying concentrations of the ingredient. The simulations, based on urinary excretion data from human bathing studies, predict a lack of potential for accumulation of the ingredient in humans. Subsequent submissions from the same manufacturer included a review article on the toxicity of chloroxylenol (Ref. 19), a retrospective analysis of the value of chronic animal toxicology studies of pharmaceutical compounds (Ref. 20), and copies of all available toxicity data for chloroxylenol (Ref. 21). Included in the toxicity data was a kinetic analysis (Ref. 37) of data from human and animal studies of the ingredient previously submitted to the agency that also predicts that accumulation in humans is not likely to occur at reasonable exposure levels. Based on the above data and information, the manufacturer requested that the agency reconsider the necessity of a long-term animal study. In response to the manufacturer's request, a public meeting was held to discuss the available toxicity data for chloroxylenol. At that meeting, the agency noted that many of the subchronic studies of the ingredient are of limited usefulness because they were conducted using a formulated product that contained isopropyl alcohol, turpineols, and castor oil soap in addition to chloroxylenol. The kinetic model used in the studies was considered inappropriate. A one-compartment model, as used in the analysis, is not relevant to chloroxylenol due to its lipophilic nature. The agency's detailed comments are on file in the Dockets Management Branch (Refs. 38 and 39).

After considering the manufacturer's comments and evaluating the data available at the time, the agency concluded that the information was not adequate to characterize the level of absorption, the distribution, the metabolism, and the excretion of chloroxylenol following topical administration. In a 1988 letter to the manufacturer (Ref. 40), the agency stated: (1) That data from the human bathing studies reviewed are highly variable (absorption 0.5 to 15.7 percent), (2) the analytical methodology used in the studies had not been validated and (3) that the small number of subjects included in the studies made it difficult to draw meaningful conclusions from the reported results. The agency commented further that submitted accumulation predictions were not adequate to define the toxicity that might occur with repeated exposure to the ingredient because no data have been submitted to support or validate the model's assumptions in characterizing exposure and stated that additional data are needed to justify, support, and verify the assumptions and data used in the predictions. Pointing out that accumulation is not the sole issue of long-term toxicity, the agency asserted that long-term toxicity may be related to repeated daily exposure to low levels of the ingredient over a lifetime.

In that same letter, the agency stated that it had reexamined the necessity for a long-term animal study based on the manufacturer's assertion that use of the ingredient as an antiseptic handwash and surgical scrub should be regarded as repeated use to a limited area of the body, and had concluded that data from additional short-term studies conducted under actual use conditions (i.e., where abrasion is followed by occlusion, with the level of absorption, distribution, metabolism, and elimination of the ingredient being shown under these conditions) could provide adequate information to determine whether or not a long-term animal study is necessary. Protocols for a pharmacokinetic surgical scrub study to develop such data were submitted to the agency (Refs. 41 and 42); however, to date the agency has not received any data from such a study. The agency's detailed comments are on file in the Dockets Management Branch (Refs. 43 and 44).

More recently, the agency received additional data pertaining to the safety of chloroxylenol from another manufacturer (Ref. 30). The data included an assessment of the ingredient's mutagenic potential by a series of in vitro and in vivo assays (Ames test, unscheduled DNA synthesis in rat primary hepatocytes, chromosomal aberrations in Chinese hamster ovary cells, and an in vivo mouse micronucleus assay). The data also included a dose range-finding study for a teratology study of the ingredient in rats and the subsequent teratology study.

Two of the four mutagenicity assays included in the submission yielded suspect or equivocal results. The in vitro administration of 19, 38, 75, and 150 micrograms per milliliter (μg/mL) doses of chloroxylenol to Chinese hamster ovary cells produced a statistically significant increase relative to the solvent control in the mean number of chromosome aberrations per cell at the 75 and 150 μg/mL dose level both in the presence and absence of

metabolic activation. Statistically significant increases in the percent of aberrant cells were also seen at the 75 µg/mL dose in the absence of metabolic activation and at the 75 and 150 µg/mL doses in the presence of metabolic activation. No dose response was apparent in either the activated or nonactivated systems. The investigator concluded that the results were equivocal in the nonactivated test system and suspect in the activated test system.

The results of the in vivo mouse micronucleus assay demonstrated a statistically significant increase in micronucleated polychromatic erythrocytes in female mice 24 and 72 hours after oral dosing with 250 and 833 milligrams per kilogram (mg/kg) doses of chloroxylenol. However, no dose response was apparent. The investigator considered the results to be a statistical anomaly based on unusually low mean micronucleus values in the negative control group and the lack of a dose response. However, the agency believes that because the observed increases were significantly elevated over those of the negative controls ($p \leq 0.01$) and were reproducible at two dose levels, these results should be considered equivocal. The manufacturer has provided additional information (Ref. 45) in response to the agency's interpretation of the results of the mouse micronucleus assay. However, the agency continues to believe that reliance on data from historical controls is inappropriate and has not changed its position on the data. The agency's detailed comments are on file in the Dockets Management Branch (Refs. 46 and 47).

In light of the new data (Ref. 30) and the issues that they raise, the agency has again reexamined the data requirements necessary to support the safe chronic use of this ingredient. The agency finds it necessary to broaden the additional testing requirements in order to clearly assess potential risks associated with chronic use of chloroxylenol. Therefore, data obtained from the following are necessary: (1) Human studies conducted under maximal use conditions, i.e., repeated use as a surgical scrub use where abrasion is followed by occlusion, characterizing the level of absorption, the distribution, metabolism, and elimination of the ingredient, (2) a lifetime dermal carcinogenicity study (up to 2 years) in mice, and (3) an appropriate human epidemiological study performed to determine the effects on health-care professionals in countries, such as England, where the ingredient has been used extensively for a long period of time are necessary. Further, in order to relate the data derived from the chronic animal study to humans, the lifetime dermal carcinogenicity study should also include concomitant absorption, distribution, metabolism, and excretion studies. A protocol for an 18-month dermal carcinogenicity study has been submitted to the agency (Ref. 48). The agency's detailed comments and evaluation of the data and protocol are on file in the Dockets Management Branch (Ref. 47).

Regarding the effectiveness of chloroxylenol, the agency stated the following in the previous tentative final monograph: "Claims for broad spectrum activity have been made * * *; however, the Commissioner finds that inadequate effectiveness data were submitted. Many studies were old and not performed with modern antiseptic testing procedures. * * * effectiveness testing both in vitro and in vivo should be done in accordance with the Guidelines" (43 FR 1238).

The applicable effectiveness data submitted by the comments were derived from in vivo and in vitro studies (Refs. 1 through 7 and 13 through 16), along with data subsequently submitted under the "feedback" procedures (Refs. 22 through 28 and 50).

Data from in vivo glove juice studies (Refs. 1, 2, 19, and 50) demonstrated the antiseptic activity of chloroxylenol in a range of 3 to 3.75 percent when formulated in an aqueous surfactant vehicle. Chloroxylenol formulations are substantive in their activity, i.e., they do not produce an initial high reduction in the number of bacteria but after repeated use (routine use), they reduce the baseline number of bacteria and suppress bacterial growth for 6 hours. In vivo data for surgical hand scrub products containing chloroxylenol at concentrations lower than 3 percent are insufficient. Aqueous solutions of chloroxylenol in a pine oil vehicle (1:40 dilution of Dettol®) consistently reduced more than 99 percent *Staphylococcus aureus* (*S. aureus*) from the hands of test subjects (Ref. 25).

In vivo cup scrubbing and other appropriate data (Refs. 22, 23, and 24) indicate that chloroxylenol, in 70 percent alcohol, is fast acting as a patient preoperative skin preparation. However, alcohol itself meets the criteria for a preoperative skin preparation and is a significant contributor for fast acting contaminant reduction. The data are not sufficient to demonstrate that chloroxylenol in this formulation contributes to the total antimicrobial effect.

In vitro study data (Refs. 1, 3, 4, 5, 13 14, 16, and 26) show that chloroxylenol in various vehicles is effective against gram-negative bacteria, i.e., *Escherichia coli* (*E. coli*), *P. aeruginosa*, *Proteus vulgaris*, and *Klebsiella aerogenes* (*K. aerogenes*). This anti-gram-negative activity is formulation dependent. Tested aqueous solutions of pure chloroxylenol with no other additives show that low concentrations (0.3 mg/mL) reduced 95 percent of some *Pseudomonas* in 10 minutes.

Data regarding the antiseptic activity of chloroxylenol itself are not adequate. While the data are considered sufficient to support in vitro effectiveness for the finished products, the available data are inadequate to show the contribution of the chloroxylenol. Because these finished products contain several additional ingredients, e.g., surfactants, isopropanol, pine oil, or ethylenediaminetetraacetic acid (EDTA), which contributed substantial germicidal activity, conclusions regarding chloroxylenol's active contribution to the product's efficacy cannot be supported. The agency's detailed comments and evaluations of the submitted data are on file in the Dockets Management Branch (Refs. 51 and 52). One manufacturer has responded to FDA's concern and provided additional data (Ref. 53). These data are currently being reviewed by the agency and will be discussed in the final rule for these drug products. In summary, the data are sufficient to support the in vitro and in vivo effectiveness of the formulations tested. However, additional data are needed to demonstrate that chloroxylenol contributes to the activity of these formulations. In addition, data from glove juice studies indicate that the antimicrobial activity of chloroxylenol is substantive in nature and does not produce an initial high reduction of bacteria, but that repeated use of the ingredient will produce a reduction in bacteria as well as a suppression of the baseline number of bacteria of the normal skin flora for 6 hours. As discussed in section I.N., comment 28, the agency is proposing that all antimicrobial products indicated for use as a surgical scrub or health-care personnel handwash be able to demonstrate an immediate reduction in bacteria and is inviting comment on the use of substantive antimicrobials in health-care antiseptic drug products.

The agency, therefore, is proposing that chloroxylenol at the concentrations evaluated (0.24 percent to 3.75 percent) be classified as Category I for safety and Category III for effectiveness for short-term use as a patient preoperative skin preparation and in Category III for safety and effectiveness for long-term uses, i.e., antiseptic handwash or health-care

personnel handwash and surgical hand scrub. The existing data are not adequate to extrapolate and assess the chronic toxicity of chloroxylenol for long-term use. Before chloroxylenol may be generally recognized as effective, the agency recommends that appropriate in vitro and in vivo effectiveness data be submitted. The data should include results obtained from both in vitro and in vivo tests as described in the testing procedures below. (See section I.N., comment 28.)

References

(1) Unpublished Clinical Safety and Effectiveness Studies on Aqueous Soap Formulations, Comment No. 0B7, Docket No. 75N–0183, Dockets Management Branch.

(a) Controlled Clinical Study Comparing the Activity of Fresh, Camay Soap, and Phisohex Against the Natural Bacterial Flora of the Hand.

(b) Antimicrobial Activity of PCMX, Triclosan, and TCC.

(c) Repeated Insult Patch Testing of Fresh Soap.

(2) Unpublished Nonclinical and Clinical Studies, and Protocols, Comment No. C96, Docket No. 75N–0183, Dockets Management Branch.

(a) Part I: PCMX Toxicosis, final reports of completed studies, interim reports of incomplete studies, and Preclinical Testing Protocol.

(b) Part II: Complete Reports on Clinical Safety and Efficacy and In Vitro Efficacy Studies.

(3) Unpublished Clinical Effectiveness Studies on Aqueous Soap Formulations, Comment No. C122, Docket No. 75N–0183, Dockets Management Branch.

(a) Protocol and Results of a Glove Juice Hand Washing Test Performed with PHLO Antimicrobial Skin Cleanser.

(b) Results of a Zone of Inhibition and Assay Performed on Aged Samples of PHLC Antimicrobial Skin Cleanser.

(4) Unpublished Clinical Safety and Effectiveness Studies on Aqueous Soap Formulations, Comment No. C123, Docket No. 75N–0183, Dockets Management Branch.

(a) Bactericidal Activity of Envair Antiseptic Hand Soap.

(b) Dermal Irritation Study.

(c) Insult Patch Test.

(d) Bacterial Kill Test.

(e) Hand-wash Effectiveness Test.

(5) Unpublished In Vitro Effectiveness Studies Performed on Aqueous Soap Solutions, Comment No. C125, Docket No. 75N–0183, Dockets Management Branch.

(a) AOAC Available Chlorine Germicidal Equivalent Concentration Test.

(b) The Antimicrobial Activity of a Sample.

(6) Published and Unpublished Nonclinical and Clinical Safety Studies, Comment No. SUP11, Docket No. 75N–0183, Dockets Management Branch.

(7) Comment No. SUP12, Docket No. 75N–0183, Dockets Management Branch.

(8) Unpublished Clinical Safety an Effectiveness Studies, Comment No. SUP10, Docket No. 75N–0183, Dockets Management Branch.

(a) The Effects of Vaseline Petroleum Jelly and Vaseline First Aid Carbolated Petroleum Jelly on Epidermal Wound Healing—A Controlled Clinical Laboratory Study, April 29, 1976.

(b) The Effect of Vaseline Petroleum Jelly and Vaseline First Aid Carbolated Petroleum Jelly on Healing of Experimental Skin Wounds, January 13, 1977.

(9) Bradbury, S. J., and J. Hayden, "Effect of Dettol® Wound Healing in Rats," Report No. RC 76132, unpublished study, Comment No. SUP5, Docket No. 75N–0183, Dockets Management Branch.

(10) Bradbury, S.J., and E.J. Hayden, "Dettol® Wound Healing," unpublished study, Project No. RC 1081, 1978, Comment No. SUP12, Docket No. 75N–0183, Dockets Management Branch.

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(32) Letter from C. Rose, Pennwalt Corporation, to W.E. Gilbertson, FDA, coded LET59, Docket No. 75N–0183, Dockets Management Branch.

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(39) Memorandum of meeting between representatives of Dexide, Inc., Ferro Corp., and FDA, coded MM11, Docket No. 75N–0183, Dockets Management Branch.

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(41) Comment No. C165, Docket No. 75N–0183, Dockets Management Branch.

(42) Comment No. SUP51, Docket No. 75N–0183, Dockets Management Branch.

(43) Letter from W. E. Gilbertson, FDA, to M. K. Bruch, Dexide, Inc., coded LET93, Docket No. 75N–0183, Dockets Management Branch.

(44) Memorandum of meeting between representatives of Dexide, Inc., Ferro Corp., and FDA, coded MM15, Docket No. 75N–0183, Dockets Management Branch.

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(46) Letter from W. E. Gilbertson, FDA, to G. R. Kramzar, NIPA Laboratories, Inc., coded LET97, Docket No. 75N–0183, Dockets Management Branch.

(47) Letter from W. E. Gilbertson, FDA to G. R. Kramzar, NIPA Laboratories, Inc., coded C174, Docket No. 75N–0183, Dockets Management Branch.

(48) Comment No. C173, Docket No. 75N-0183, Dockets Management Branch.

(49) Comment No. LET65, vol. 4, 5, and 6, Docket No. 75N–0183, Dockets Management Branch.

(50) McCracken, A., "Effectiveness of Ultradex Scrub Sponge Determined in a Clinical Setting," unpublished study, coded LET65, vol. 6, Docket No. 75N–0183, Dockets Management Branch.

(51) Letter from W. E. Gilbertson, FDA, to M. K. Bruch, Dexide, Inc., coded LET87, Docket No. 75N–0183, Dockets Management Branch.

(52) Letter from W. E. Gilbertson, FDA, to M. K. Bruch, Dexide, Inc., coded LET90, Docket No. 75N–0183, Dockets Management Branch.

(53) Letter from M. K. Bruch, Dexide, Inc., to W. E. Gilbertson, FDA, coded LET91, Docket No. 75N–0183, Dockets Management Branch.

H. Comment on Hexachlorophene

13. One comment urged reconsideration of hexachlorophene as an OTC "handwashing agent and antimicrobial skin cleanser for use in the hospital, doctor's office, and by adult consumers." The comment stated that adequate data to support Category I status were submitted in response to the advance notice of proposed rulemaking, but were only superficially discussed by the agency in comment 61 of the tentative final monograph. (See the **Federal Register** of January 6, 1978, 43 FR 1210 at 1220.) The comment submitted additional data to support the safety of hexachlorophene, including a retrospective study on 3 percent hexachlorophene in baby bathing (Ref. 1) and a study of hexachlorophene blood levels in infants receiving routine antiseptic skin care (Ref. 2). The comment also included a comprehensive review article on the safety and effectiveness of hexachlorophene (Ref. 3).

The agency has reevaluated the data discussed in comment 61 in the tentative final monograph (43 FR 1220) and evaluated the new data, and has determined that the data do not warrant changing the classification of hexachlorophene as a prescription drug. The infant data (Refs. 1 and 2) were discussed in detail in the tentative final monograph for OTC antimicrobial diaper rash drug products (55 FR 25246 at 25261 to 25263).

Summaries of handwash studies were also submitted, but no data were included. In one study, 3 percent hexachlorophene was tested as a surgical scrub under exaggerated use conditions (Ref. 4). Subjects (number not specified) washed their hands and forearms in 20 mL hexachlorophene for 10 minutes, 5 times daily, 6 days a week for a total of 58 days. No signs of toxicity were reported. The blood levels of hexachlorophene reached a plateau within 3 days at mean levels of 0.07 μg/mL.

The agency believes that it would be necessary to test a very large group of subjects (the number of subjects required to obtain a statistically significant result) with a variety of skin conditions to determine the true degree of absorption. A similar study reviewed by the Panel (39 FR 33103 at 33118) reported blood levels of 0.5 μg/mL or higher.

In the other study, subjects washed their hands and face three times daily for 3 weeks with either 2 or 5 mL of 3 percent hexachlorophene (Ref. 4). Blood concentrations reached a plateau within 7 days at mean levels of 0.21 μg/mL for the 2-mL group and 0.22 μg/mL for the 5-mL group.

Other additional data contained only a brief summary of the historical use of hexachlorophene and primarily cited publications in the medical literature (Ref. 5). The references provided no new information. Consequently, the agency has determined that hexachlorophene will continue on prescription status subject to the existing regulation in 21 CFR 250.250.

In order for hexachlorophene to be switched to OTC status, the concerns expressed by the Antimicrobial I Panel that hexachlorophene does not have an adequate margin of safety for OTC use (39 FR 33103 at 33117) should be addressed. After reviewing the submitted data, the agency concludes that the safety of this ingredient for OTC use on infants has not been demonstrated. For OTC status for use by adults, any further submission of data should specifically address the safe OTC use of hexachlorophene in adults.

Based upon the discussion above, the agency is proposing that hexachlorophene remain available by prescription only, except when used as a preservative at concentrations of 0.1 percent or less.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 6).

References

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(2) Plueckhahn, V. D., "Blood Hexachlorophene Concentrations in New-Born Infants Undergoing Routine Antiseptic Skin Care with a 3% Hexachlorophene Emulsion," unpublished study contained in SUP13, Docket No. 75N–0183, Dockets Management Branch.

(3) Plueckhahn, V. D., "Infant Antiseptic Skin Care with Hexachlorophene Emulsions and Powders," unpublished study contained in SUP28, Docket No. 75N–0183, Dockets Management Branch.

(4) Comment No. SUP13, Docket No. 75N–0183, Dockets Management Branch.

(5) Comment No. C116, Docket No. 75N–0183, Dockets Management Branch.

(6) Letter from W. E. Gilbertson, FDA, to G. S. Goldstein, Sterling Drug Inc., coded LET63, Docket No. 75N–0183, Dockets Management Branch.

I. Comments on Iodine and Iodophors

14. One comment pointed out that poloxamer-iodine complex appeared to be incorrectly included in the Category II list under "health-care personnel handwash" (43 FR 1210 at 1227), while it is properly listed in Category III for use as a "health-care personnel handwash" (43 FR 1210 at 1229). The comment stated that deletion from the Category II list would correct the error.

The agency concurs with the comment that poloxamer-iodine complex for use as a health-care personnel handwash was incorrectly listed as Category II (43 FR 1227) and that the listing as Category III (43 FR 1229) was correct.

15. One comment submitted data on the safety and effectiveness of a "mixed iodophor" consisting of iodine complexed by ammonium ether sulfate and polyoxyethylene sorbitan monolaurate (Ref. 1). The comment stated that this information had been previously submitted in May 1974, but that the ingredient had not been mentioned in the Panel's report or in the agency's proposed monograph and requested that the agency include it in the monograph. The comment pointed out that the iodophor, formulated as a liquid hand scrub, is intended for use by surgeons, food handlers, and others for whom reduced bacterial skin flora is of public health significance.

Regarding the comment's statement that the data were previously submitted,

the agency has no record of any submission of these data in 1974. Because this hand scrub was not previously reviewed or categorized as an OTC topical antimicrobial drug product, the agency reviewed the product's marketing history and considers it appropriate to include this product in the OTC drug review. The agency has evaluated the data submitted by the comment (Ref. 1) and determined that iodine complexed by ammonium ether sulfate and polyoxyethylene sorbitan monolaurate is safe for use as a surgical hand scrub and health-care personnel handwash, but that there are insufficient data available to determine its effectiveness for these uses. Therefore, the ingredient is being classified in Category III.

The data included several studies on the absorption of the iodine complex, blood levels of iodine, and the systemic toxicity of the iodine complex. Protein-bound iodine (PBI) and iodine blood levels in rabbits were determined following two studies of acute dermal applications. In the first study, either 2 or 5 mL/kilogram (kg) of the test iodine complex was applied to the shaved backs of rabbits in one experiment. The method of occlusion, if any, was not stated, but the test material was washed off after 24 hours. In another experiment, 2 mL/kg of the test iodine complex was compared with a povidone-iodine complex and both were applied as in the first experiment. PBI and total iodine in blood were determined at 0, 24, and 48 hours in both experiments. In all treated animals, the level of PBI was extremely high at certain times, primarily at 24 hours. Animals receiving the higher dose of iodine complex in the first experiment seemed to return to normal sooner than those receiving the lower dose. All animals returned to normal by 14 days. For purposes of comparison, the second experiment showed that serum total iodine increased from 1.4 to 30.7 milligrams/deciliter (mg/dL) in the test iodine complex group compared to from 1.23 to 37.9 mg/dL in the povidone-iodine group in the 24 hours that the application remained on. In the second study, 5 mL/kg of the test iodine complex was applied to the shaved backs of two groups of five rabbits each. In one group the shaved backs were occluded for 24 hours and in the other group, the shaved backs were scrubbed for 10 minutes followed by rinsing and occlusion. An additional group served as an untreated control group. Blood samples for iodine determinations were taken at 0, 24, and 48 hours and at 14 days. All five animals in the group in which the iodine complex remained occluded on intact skin for 24 hours had markedly elevated levels of PBI and iodine at both 24 and 48 hours, but were only slightly above normal at 14 days. For the 10-minute scrub animals, the PBI levels were increased in two of five animals at 24 hours, slightly in all five animals at 48 hours, and were normal at 14 days.

A study to determine the effect on blood PBI levels of a routine scrubbing procedure in which exposure to the iodine complex exceeded normal use showed no alteration in PBI levels in four humans who scrubbed twice daily (each scrub consisting of two 5 minute hand washes with 5 mL) for 26 consecutive days. Also, no irritation was observed. In a similar study in which the subjects wore gloves for 2 hours after each scrub, PBI levels were not increased, but total iodine was slightly increased. In two subjects, this increase was greater in the middle of the study, but the total iodine blood levels were near normal by the end of the study.

A dermal absorption study in which the shaved backs of four monkeys were rubbed with 0.17 mL/kg of radioactive iodine complex for 10 minutes, rinsed, wrapped for 2 hours, and the animals sacrificed after 24 hours, revealed that less than 0.1 percent of the application was recovered in the thyroid, the target organ for iodine.

A 90-day sub-acute dermal toxicity study was conducted in three groups of monkeys divided into one control group and two test groups. One test group was scrubbed once for 10 minutes daily with 0.17 mL/kg of the iodine surgical scrub detergent product and the second group was scrubbed three times with 0.34 mL/kg (once for 10 minutes and twice for 3 minutes each day). To simulate the wearing of surgical gloves, the treated area of each animal, which consisted of a shaved area of the back equivalent to about 10 percent of the body area, was wrapped with a rubber dam for 30 to 90 minutes. The study lasted 13 weeks during which the animals were monitored. Neither test group showed any effects of iodophor treatment except elevated PBI levels in the high dose group, which peaked at one month. Also, there was no significant effect on the thyroid in the treated groups.

The agency believes this iodine complex is safe for humans based on the data from human, rabbit, and monkey studies. Test data showed very little iodine absorption when the product was used as a scrub, negligible uptake (following acute dermal application of radioactive iodine complex) by the thyroid in monkeys, and an unchanged thyroid weight in test groups of monkeys following 90 days of sub-acute applications of the iodine complex.

The comment submitted data from one clinical study for evaluating effectiveness as a surgical hand scrub but did not provide the testing protocol used. Five subjects scrubbed three times daily for 5 days with the iodophor formulation (containing 1.1 percent iodine). Four subjects completed the study. Surgical gloves were worn for 2 hours after the first wash of the day. Subjects' hands were sampled once each day at the end of the 2-hour gloved period using a single-basin Cade method. The initial sampling was used to establish a baseline microbial count for each subject. Study results were reported as the number of organisms per mL of basin water and the percent reduction in the number of organisms recovered. The reduction in the bacterial population ranged from 89 to 98 percent on the first day. By the fifth day, the reduction ranged from 99 to 100 percent. Similar results were obtained in a comparative study on six subjects using povidone-iodine.

Although it is clear that the test used was not the glove juice test which is described in the antimicrobial tentative final monograph (43 FR 1210 at 1242), alternative methods may be acceptable. However, because of the small number of subjects included in the study, the data are not sufficient to support the Category I classification of this ingredient for use as a surgical hand scrub. Additional studies, of the type described in § 333.470(b)(1) of this amended tentative final monograph, are necessary to support the effectiveness of this surfactant iodine complex for this use.

In the previous tentative final monograph (43 FR 1235), the agency recognized that elemental iodine complexed with a surfactant type "carrier" molecule reduces the amount of immediate "free" iodine, because most of the formulated iodine is bound in the complex. Effectiveness of all iodophors is dependent on the release of free iodine as the active agent from the complexing molecule which acts only as a carrier. The agency acknowledges that iodine complexed with a surfactant is an acceptable way of presenting iodine as an antimicrobial agent to the skin. However, because most of the formulated iodine may be tied up in the complex and because the information submitted by the comment to support in vitro efficacy (Ref. 2) dealt only with aqueous and/or tincture solutions of free iodine, testing of the complete formulation is necessary to judge the importance of formulation on the release of the active ingredient and,

thus, its influence on aspects of effectiveness.

Based on the data submitted, the agency concludes that iodine complexed by ammonium ether sulfate and polyoxyethylene sorbitan monolaurate is safe but additional data from appropriate studies are needed to establish general recognition of effectiveness for use as a surgical hand scrub and health-care personnel handwash. The data should include results obtained from both in vitro and in vivo testing procedures. (See section I.N., comment 28.)

References

(1) Unpublished Nonclinical and Clinical Studies on V.I.S., Vestal Iodine Scrub (iodine complexed by ammonium ether sulfate and polyoxyethylene sorbitan monolaurate), Comment No. C106, Docket No. 75N–0183, Dockets Management Branch.

(a) Acute Dermal Toxicity in Rabbits.

(b) Acute Dermal Application—Rabbits.

(c) Determination of the Influence of Scrubbing with Vestal Iodine Surgical Scrub Detergent on the Protein Bound Iodine Level of the Blood.

(d) Determination of the Influence of Scrubbing with Vestal Iodine Surgical Scrub Detergent on the Protein Bound Iodine and Total Serum Iodine Levels in the Blood.

(e) Percutaneous Absorption of Iodine in Monkeys from the Dermal Application of an Iodine Surgical Scrub Detergent.

(f) Three Month Sub-Acute Dermal Toxicity Study in Monkeys with Vestal Iodine Scrub Detergent.

(g) Iodine Surgical Scrub Detergent, Surgical Hand Scrub Study in Five Human Test Subjects.

(2) Gershenfeld, L., "Iodine," in "Disinfection, Sterilization, and Preservation" 1st ed., Lee and Febiger, Philadelphia, pp. 329–347, 1968.

16. Several comments objected to the warning proposed for the professional labeling for povidone-iodine and iodophor-surfactant products: "Caution: Do not use this product in the presence of starch-containing products. Starch can adsorb iodophors and the resulting complex can cause serosal adhesions (abnormal union of the serous membranes) and other undesirable effects in the body" (43 FR 1210 at 1221). The comments pointed out that the study by Goodrich, Prine, and Wilson (Ref. 1) on which the warning is based is not well controlled, is rudimentary, and lacks rigorous testing that produces evidence which can be statistically analyzed. The comments contended that this article is not sufficient basis for the warning. The comments requested that the impact of the article by Goodrich, Prine, and Wilson on the labeling of nonsurfactant iodophors be reevaluated and that povidone-iodine be exempt from the required warning relating to contact of starch and iodophors. One comment stated that there are numerous papers in the literature describing the antiadhesive effect of povidone and povidone-iodine and submitted nine references dealing with humans and animals that support an antiadhesive effect when povidone or povidone-iodine is used in intraperitoneal surgery (Ref. 2). Another comment explained that starch is well known for producing granuloma and that every package of surgeons' gloves carries a warning statement to the effect that the outside of the gloves must be cleansed of starch powder prior to use. The comment concluded that FDA should require a warning label on the gloves, but not on products containing the drug.

FDA has reevaluated the article by Goodrich et al. (Ref. 1), considered the additional cited references (Ref. 2), and examined current policy on the labeling of United States Pharmacopeia (U.S.P.) Absorbable Dusting Powder (cornstarch). Goodrich, Prine, and Wilson (Ref. 1) provide data from observations and arbitrary scoring of adhesions after intraperitoneal injection into 4 groups of 13 adult female mice with: (1) Powdered starch suspended in 1.5 mL of normal saline, (2) powdered starch treated with 5 mL of an iodophor and washed three times in saline before resuspension in 1.5 mL normal saline, (3) powdered starch treated with 5 mL of a 10-percent solution of surfactant washed three times in saline and resuspended in 1.5 mL of normal saline and (4) normal saline (control animals). The data do not indicate any significant difference between suspensions of the surfactant mixed with starch and the surfactant-iodophor mixed with starch. The agency's policy on the labeling of surgical gloves treated with Absorbable Dusting Powder U.S.P., determined upon evidence presented during the Drug Efficacy Study Implementation, was published in the **Federal Register** of May 25, 1971 (36 FR 9475). The agency requires the following statement on surgical gloves treated with Absorbable Dusting Powder U.S.P.: "Caution: after donning, remove powder by wiping gloves thoroughly with a sterile wet sponge, sterile wet towel, or other effective method." Products containing Absorbable Dusting Powder U.S.P. for lubricating surgical gloves were formerly classified as new drugs, but are now regarded as transitional devices, for which premarket approval is required under the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (42 FR 63472 at 63474). FDA's Center for Devices and Radiological Health is establishing categories for all surgical devices, including surgical gloves lubricated with powdered starch. Any changes in the labeling for this class of products will be dealt with in a separate rulemaking procedure and separate **Federal Register** notice.

The agency believes that the user's removal of dusting powder from surgical medical devices (rubber goods) treated with Absorbable Dusting Powder U.S.P. decreases the incidence of adhesions and is not persuaded that the data in the article by Goodrich, Prine, and Wilson provide a sufficient scientific basis for a warning label. Therefore, the warning about the interaction of iodophors and starch-containing products proposed in comment 66 of the previous tentative final monograph is not included in this amended tentative final monograph.

References

(1) Goodrich, E. O., J. R. Prine, and J. S. Wilson, "Iodized Starch Granules as a Cause of Starch Peritonitis," *Surgical Forum*, 25:372–374, 1974.

(2) Nonclinical and Clinical Safety Studies on Postoperative Observations of Abrasions, Comment No. C111, vol. 4, tabs 6–14, Docket No. 75N–0183, Dockets Management Branch.

17. A number of comments submitted new data (Ref. 1) to establish that povidone-iodine is safe and effective as a topical antimicrobial drug. The comments requested that povidone-iodine be reclassified from Category III to Category I as a topical antimicrobial ingredient for use as an antimicrobial soap, health-care personnel handwash, surgical hand scrub, patient preoperative skin preparation, skin antiseptic, skin wound cleanser, and skin wound protectant.

As discussed earlier in this document, this amended tentative final monograph addresses only topical antiseptics for health-care antiseptic uses as a surgical hand scrub, antiseptic handwash or health-care personnel handwash, and patient preoperative skin preparation. As discussed in section I.B., comment 5, antimicrobial soaps are no longer included in this rulemaking. The agency addressed the other use categories mentioned in the comment in a separate **Federal Register** notice for OTC first aid antiseptic drug products (56 FR 33644). As discussed in comment 38 of that document (56 FR 33660), FDA has tentatively concluded that povidone-iodine should be classified in Category I for use as a first aid antiseptic (formerly designated skin antiseptic, skin wound cleanser, and skin wound protectant).

The agency has considered the new data submitted and other information in

support of the request to reclassify povidone-iodine from Category III to Category I. On the basis of these data and information, the agency tentatively concludes that povidone-iodine should be reclassified from Category III to Category I as a topical antiseptic ingredient for use in surgical hand scrub, patient preoperative skin preparation, and health-care personnel or antiseptic handwash drug products.

The general safety aspects of povidone-iodine that concerned the agency in the previous tentative final monograph (43 FR 1210 at 1234 to 1236) are addressed elsewhere as follows: (1) The effect of povidone-iodine on wound healing. Based upon submitted data, the agency concluded in the first aid antiseptic segment of this rulemaking that non-surfactant iodophor products (povidone-iodine) do not delay wound healing. See comment 42 of that document (56 FR 33644 at 33662). Also, the Advisory Review Panel on OTC Antimicrobial II Drug Products reviewed povidone-iodine's effect on wound healing in its report on topical antifungal drug products and concluded that the drug did not affect wound healing (47 FR 12480 at 12545). (2) The effect of povidone-iodine on thyroid function. In comment 41 of the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33661), the agency discusses studies that indicate that topically applied povidone-iodine does not cause thyroid dysfunction. (3) The proposed warning about the interaction of starch-containing products with iodophors resulting in serosal adhesions and other undesirable effects, i.e., "Caution: Do not use this product in the presence of starch-containing products. Starch can adsorb iodophors and the resulting complex can cause serosal adhesions (abnormal union of the serous membranes) and other undesirable effects in the body" (43 FR 1210 at 1221). The agency has reevaluated the proposal and decided that the warning is not supported by the data. (See section I.I., comment 16.) (4) The agency's concern regarding molecular weights of povidone-iodine greater than 35,000 daltons not being excreted by the kidney and causing lymph node changes. In section I.I., comment 18, the agency discusses a previously proposed warning regarding this subject and determines, based on more recent data, that larger povidone-iodine molecules are not a risk when the product is limited to the topical uses included in this tentative final monograph.

The agency's concern about the need for expiration dates (not to exceed 2 years after manufacture) because of the lack of stability data for several iodophor preparations, which relates to the effectiveness of the product, can be satisfied by compliance with the current good manufacturing practices regulations (21 CFR parts 210 and 211). These regulations include, among other things, requirements regarding stability testing and expiration dating (see §§ 211.137 and 211.166). Therefore, as discussed in comment 40 of the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33661), data on the stability of povidone-iodine and the proposed 2-year expiration date are no longer considered needed in this rulemaking proceeding.

A second agency concern relating to effectiveness was the rate of release of "free" iodine from the complex and whether there was evidence of germicidal activity over a period of time in clinical application (43 FR 1210 at 1235). As discussed in the tentative final monograph for OTC topical acne drug products (comment 5, 50 FR 2172 at 2173), iodine is released from the povidone-iodine complex within milliseconds, thus resolving this concern.

With regard to the effectiveness of health-care antiseptic uses subject to this rulemaking, the agency has reviewed the data and information on povidone-iodine's germicidal in vitro and antiseptic in vivo effectiveness (Refs. 1 through 19) and concludes that the data are sufficient to reclassify this ingredient from Category III to Category I.

A series of in vitro controlled studies (Ref. 1–C133, Volume 1) included a broad spectrum of test micro-organisms which were associated with between 40 to 60 percent of the nosocomial infections in the urinary tract, surgical wounds, pneumonia, and bloodstream, reported by the National Nosocomial Infections Surveillance System (NNIS) for the period from January 1985 to August 1988 (Ref. 2). In most instances, these test micro-organisms, as proposed in § 333.470(a)(1)(ii) (see section I.C., comment 6), were killed after 0.5 to 5 minutes exposure to povidone-iodine. A minimum inhibitory concentration (MIC) study (Ref. 1–C133) using 30 cultures, both American Type Culture Collection (ATCC) and recent skin isolates, was also included in this series of in vitro studies. The results indicated a range for MIC from 87 parts per million (ppm) to 492 ppm for dilutions of povidone-iodine solution and 83 ppm to 476 ppm for dilutions of povidone-iodine surgical scrub depending on the test micro-organism. Tests with controls, neutralizer, and organic load using a serial dilution method were included in the study.

Gocke, Ponticas, and Pollack (Ref. 3) evaluated the susceptibility of 230 clinical isolates from blood, urine, sputum, and wound cultures to the bacteriocidal activity of povidone-iodine. These clinical isolates contained over half the organisms included in § 333.470(a)(1)(ii). Results indicated that 106 of the 230 organisms tested (46 percent) were killed when 1 mL of a standardized suspension containing 10^8 organisms was exposed to a 10 percent povidone-iodine solution for 15 seconds. Povidone-iodine showed its highest activity against gram-negative isolates, with 72 of the 94 isolates (75 percent) being killed after a 15-second exposure. Only 34 of the 134 (25 percent) gram-positive isolates were killed under the same conditions. However, further testing of organisms not killed after a 15-second exposure indicated that increases in exposure time to 120 seconds killed all of the previously "resistant" isolates. The study design incorporated the use of a neutralizer and controls.

The effectiveness of a povidone-iodine formulation on micro-organisms in a clinical setting was demonstrated by Michael (Ref. 4). The study included 100 subjects with decubitus ulcers following a spinal cord injury. Cultures of the wounds were taken prior to, during, and upon completion of a once-a-day povidone-iodine treatment. Prior to treatment, subjects had positive cultures for the following organisms: *S. aureus* (60 subjects), *Klebsiella/Enterobacter* species (20 subjects), *E. coli* (15 subjects), and *Pseudomonas* species (15 species). Following an 8-to-10 week period of treatment with povidone-iodine, cultures revealed that 90 of the 110 subjects no longer had positive cultures for these organisms.

Pereira, Lee, and Wade (Ref. 5) conducted an in vivo gloved hand test that is supportive of the effectiveness of povidone-iodine as a surgical hand scrub. They examined the effects of surgical scrub duration and type of antiseptic on the reduction of resident microbial flora. Thirty-four subjects scrubbed with a 7.5 percent povidone-iodine formulation or another antiseptic formulation using either a 5 minute initial/3 minute consecutive scrub procedure or a 3 minute initial/30 second scrub procedure. Subjects were assigned to one of four groups, and each group was assigned to one of the four treatments. Sampling was done by the glove juice method using a sampling solution containing a neutralizer. Glove juice samples were taken from both hands immediately before scrubbing

(baseline), from the nondominant hand immediately after the initial scrub, 2 hours after the initial surgical scrub but before the consecutive scrub (dominant hand), and 2 hours after one consecutive surgical scrub (dominant hand). No significant difference was found between the two durations of scrubbing with povidone-iodine. Povidone-iodine produced an immediate 1.2 $\log_{10}$ reduction on the dominant hand after an initial 5 minute scrub and a 1.0 $\log_{10}$ reduction on the dominant hand immediately after the 3 minute initial scrub. Baseline was not exceeded 2 hours after either the 5 or 3 minute scrub.

Aly and Maibach (Ref. 6) evaluated the characteristics of two antimicrobial impregnated surgical hand scrub sponge/brush drug products. The study, which included a widely used povidone-iodine impregnated surgical hand scrub sponge/brush, evaluated both the immediate and persistent effect on the resident bacterial flora of the hands plus the effect of blood on the persistent antimicrobial activity of the surgical hand scrub drug products. In the first phase of the study, 13 subjects with left and right hand baseline counts of $>10^6$ organisms were randomly assigned to perform a total of 11 scrubs with the povidone-iodine impregnated sponge/brush. Glove juice samples were taken from the right hand of each subject immediately following the first scrub of the day and from the left hand at either 3 or 6 hours. The entire procedure was repeated on test days 2 and 5. A similar procedure was used in phase two of the study, except that 2 mL of bacteriologically sterile blood was spread over the hands of 6 subjects following the initial scrub, and sampling occurred only at 3 and 6 hours. Neutralizers were incorporated into the stripping solution, diluent, and culture media. On day 1, povidone-iodine produced an immediate mean $\log_{10}$ reduction of 1.2, and baseline was not exceeded at 3 hours. On days 2 and 5, povidone-iodine produced immediate mean $\log_{10}$ reductions of 2.2 and 2.8, respectively, and bacterial counts did not exceed baseline at 6 hours. While counts for povidone-iodine approached baseline in the presence of blood, counts did not exceed baseline at 6 hours on any day.

Another study (Ref. 1–C104), employing a method similar to the effectiveness testing procedures described in proposed § 333.470(b)(2) of this amended tentative final monograph, demonstrated the effectiveness of povidone-iodine 5 percent as a health-care personnel handwash. Twenty-five consecutive handwashings were done in 10 human subjects with a 5 minute rest between washings. Before each washing the hands were dipped in broth culture containing 2.0×10^9 organisms (*Bacillus subtilis* var. *niger* ATCC 9372) per mL; the contaminant was spread up over the wrists to the forearms. Bacterial counts were done at the completion of every fifth washing by the glove juice sampling method. Both the dilution fluid and growth media incorporated a neutralizer. The transient microbial flora of the hands was reduced by an average of 5.8 logs from baseline.

Dineen (Ref. 7) used a 7.5 percent povidone-iodine formulation as a reference antiseptic in an open crossover evaluation of a health-care personnel handwash drug product. Participation in the study followed a 1-week prewash period in which study subjects used only a bland nonantiseptic soap. On day 1 of the study, samples were taken prior to contamination and again after a second contamination followed by a 15-second wash with a bland nonantiseptic soap, using the glove juice sampling method. Following the post-wash sampling, subjects washed for 5 minutes with povidone-iodine to remove any remaining inoculum. The hands of the first three subjects were contaminated with a 1 mL inoculum containing 1×10^{14} *S. marcescens, E. coli, P. aeruginosa,* and *Providentia stuartii* (*P. stuartii*). The hands of the seven other subjects were contaminated with a 1 mL inoculum containing 8×10^{14} to 2×10^{15} *S. marcescens* and *P. stuartii*. Inocula concentrations were determined each test day in a parallel experiment. On days 3 or 4 and 5, the procedure was repeated except that subjects were randomly assigned to wash with either (1) the reference antiseptic or the test preparation or (2) were crossed over to the preparation not used the previous day. In the interim between test days, subjects followed the wash and sampling procedure using only the nonantiseptic soap. The number of organisms included in the 1 mL inoculum was taken as the baseline, and all reductions were calculated on this basis. Neutralizers were incorporated in both the diluent and the culture medium. When corrected for the average log reduction produced by the nonantiseptic soap (4-$\log_{10}$), the reductions produced by povidone-iodine ranged from 7 to 9 $\log_{10}$.

Studies conducted by Ulrich (Ref. 8) and Newsom and Matthews (Ref. 9) are supportive of the effectiveness of povidone-iodine for this indication. Ulrich (Ref. 8) conducted a study using povidone-iodine 7.5 percent in 25 subjects. Both hands of each subject were contaminated with a stock culture of *Micrococcus roseus* (2.75×10^8 organisms per hand, the baseline count) and allowed to air dry for 60 seconds. This artificial hand contamination was followed by a 15-second wash with 5 mL of the povidone-iodine preparation, and this same procedure was repeated until 25 contaminations/washes had been performed. Glove fluid samples were taken after every fifth contamination/wash. Dilutions of the glove fluid were made in a sterile diluent that included a neutralizer. A neutralizer was also incorporated into the culture medium. Based on the average of both hands, the povidone-iodine preparation produced a 4.9 and a 5.2 log reduction of the transient micro-organisms from baseline by the 5th and 10th wash, respectively. By the end of the 25th wash the povidone-iodine preparation demonstrated a 5.5 $\log_{10}$ reduction from the baseline bacterial count.

Newsom and Matthews (Ref. 9) studied test solutions containing 5 or 10 percent povidone-iodine on hands artificially contaminated with an overnight culture of *E. coli*. The numbers of micro-organisms were measured before and immediately after hand disinfection with the test solution in 15 subjects. Sampling of the hands was accomplished by kneading the fingertips in a "recovery" broth that included a neutralizer. A mean 4.4 log reduction from baseline was reported for the bacterial counts taken immediately after the antiseptic wash.

Ayliffe, Babb, and Quoraishi (Ref. 10) evaluated the effect of various detergent and alcoholic antiseptic formulations (including a 7.5 percent povidone-iodine formulation) on the removal of *S. aureus, Staphylococcus saprophyticus* (*S. saprophyticus*), *P. aeruginosa,* or *E. coli* from contaminated fingertips. In one set of experiments, six subjects performed an initial wash with an unmedicated soap, followed by the inoculation of the tips of the subjects' fingers and thumbs with 0.02 mL of a broth culture containing either *S. aureus* or *P. aeruginosa*. Following contamination, subjects performed either a 30-second wash with 5 mL of a detergent or alcoholic antiseptic preparation, a 30-second wash with an unmedicated soap, or no wash at all. Bacterial sampling was accomplished by rubbing the fingers and thumbs on glass beads immersed in 100 mL of nutrient broth containing neutralizers. All treatments were tested against each organism. Results were reported as the log of the average number of viable organisms recovered from each subject. Against *S. aureus*, povidone-iodine

produced a 3.2 log reduction, which was significantly superior to the reduction achieved by the unmedicated soap. Against *P. aeruginosa*, povidone-iodine produced a 2.7 log reduction. However, this was not significantly different from the 2.2 log reduction demonstrated by the unmedicated soap.

In a second set of experiments (Ref. 10), the same authors assessed the effectiveness of three antiseptic formulations, including povidone-iodine, and an unmedicated soap in the removal of *S. aureus*, *S. saprophyticus*, or *E. coli* from contaminated fingertips. Under conditions similar to those in the previous study, povidone-iodine demonstrated a 3-log reduction in the baseline number of *S. aureus*, which was significantly superior to the log reduction demonstrated by the unmedicated soap. Povidone-iodine produced an average 2.1 log reduction in the number of *S. saprophyticus* and a 2.8 reduction in the number of *E. coli*. However, neither of these reductions was significantly different from the reductions produced by the unmedicated soap.

Rotter (Ref. 11) evaluated the influence of differences in two testing methodologies on the demonstration of the effectiveness of povidone-iodine. One test method used is the standard test method (Vienna) for the evaluation of drug products for hygienic disinfection adopted by the Austrian and German Societies for Hygiene and Microbiology. In this test model, the release of *E. coli* from the finger tips of artificially contaminated hands was determined before and after a 1-minute wash with povidone-iodine. The second model, based on agency recommendations for the testing of health-care personnel handwashes, evaluated the release of the *E. coli* from all surfaces of artificially contaminated hands by the glove juice sampling method before and after a 1 minute wash with the ingredient. These comparisons showed no significant difference in the reduction factor produced by povidone-iodine when tested with the two methods. Povidone-iodine when tested by the Vienna test method produced a 3.3 $\log_{10}$ reduction from the baseline count. When tested by the second method, the ingredient produced a 3.2 $\log_{10}$ reduction.

Rotter (Ref. 11) also used the Vienna test method to assess the effectiveness of rubbing antiseptics onto the hands versus washing with an antiseptic. Two povidone-iodine containing formulations were included in the assessment. A watery solution of povidone-iodine with 1 percent available free iodine rubbed onto the skin produced a 4 $\log_{10}$ reduction. Washing with a detergent formulation of the ingredient produced a 3.2 $\log_{10}$ reduction. However, this reduction was not statistically different from the reduction produced by washing with a nonantiseptic soap.

Rotter, Koller, and Wewalka (Ref. 12) used the Vienna test model to assess the effectiveness of a povidone-iodine liquid soap preparation (containing 0.75 percent available free iodine) for hygienic hand disinfection. The subjects' hands were contaminated by immersing them up to the mid-metacarpals in a broth culture of *E. coli*. The hands were allowed to air dry for 3 minutes prior to a pretreatment sampling. Sampling was accomplished by rubbing the finger tips of each hand for 1 minute on the bottom of a Petri dish containing a phosphate buffer sampling solution with neutralizers. After a 2-minute wash with the povidone-iodine or liquid soap followed by a 20-second rinse, the hands were again sampled. Average log values of the counts from the right and left hands of each subject were calculated, and the difference (log reduction factor) was determined. The povidone-iodine liquid soap formulation produced a 3.2 $\log_{10}$ reduction in the transient organisms.

Wade and Casewell (Ref. 13) evaluated the residual effectiveness of povidone-iodine against two clinical isolates associated with hospital outbreaks of infection. An initial determination of the survival of the test organisms on untreated hands of three subjects was made by contaminating the subjects' finger tips with either of the test organisms and sampling the individual fingers immediately after contamination and at 1, 3, 10, and 30 minutes. The subjects' hands were then pretreated by performing three 30-second washes at 5 minute intervals with various alcoholic and aqueous antiseptic test formulations, including a 7.5 percent povidone-iodine formulation and an unmedicated bar soap. The contamination and sampling procedure was repeated as before. All formulations were tested against both organisms. The median value of the log counts for the three subjects as each sampling was plotted against time. The survival curves for both organisms on hands pretreated by washing with an unmedicated soap and on hands with no pretreatment were similar. Pretreatment with povidone-iodine resulted in counts that were consistently less than for the untreated hands and for the hands pretreated by washing with an unmedicated soap and water for both organisms. After 30 minutes, hands pretreated with the povidone-iodine formulation demonstrated a 2.5 $\log_{10}$ reduction in the number of viable *Enterococcus faecium* and a 3.9 reduction in the number of viable *Enterobacter cloacae*.

The agency concludes that these data demonstrate the effectiveness of povidone-iodine 5 to 10 percent for use as a health-care personnel handwash.

Many *published* studies referenced in the submitted data and in the published literature (Refs. 1 and 14 through 19) have evaluated the effectiveness of povidone-iodine for use as a patient preoperative skin preparation. Although the procedures followed are different from those in the previous FDA testing procedures (43 FR 1210 at 1244) and from those proposed in § 333.470 of this amended tentative final monograph, the essential criteria have been met.

Georgiade et al. (Ref. 15) evaluated the effectiveness of two povidone-iodine formulations for use in the preoperative skin preparation of 150 subjects scheduled for elective surgical procedures. An initial sample for culture was taken from the unbroken skin of the operation site prior to the use of the formulations, and a baseline bacterial count was determined. Sampling was by a cup scrubbing method, using a sterile wash solution that incorporated a neutralizer. The operative site was then gently treated for 5 minutes with a povidone-iodine surgical scrub formulation and allowed to dry. Following the initial disinfection, a povidone-iodine antiseptic solution was evenly applied to the site and allowed to dry. The sample site was rinsed with sterile water and a second sample for culture was done. Upon completion of surgical procedures lasting from 30 to 180 minutes, the sample site was again cultured and sterile dressings were applied. The reported mean post-scrub reduction in the baseline number of bacteria of the sample site was 30,599 (4.5 $\log_{10}$ reduction). This reduction was maintained through the surgery as evidenced by the reported post-operative mean reduction of 30,613 organisms.

Vorherr, Vorherr, and Moss (Ref. 16) compared three antiseptic preparations (including 10 percent povidone-iodine), in 150 female subjects (50 to each preparation) for effectiveness in reducing the numbers of bacteria in the perineum and groin. The mean log reductions in bacteria after skin preparation with povidone-iodine at 10 minutes and 3 hours, respectively, were reported as 3.65/3.09 for the perineum and 3.42/2.85 for the groin. Another study by Dzubow et al. (Ref. 17) evaluated three antiseptic skin

preparations frequently used for dermatologic surgical procedures. A 60-second wipe with 1-percent povidone-iodine was performed in 14 subjects after which aerobic and anaerobic cultures were taken at 5 and 60 minutes. The aerobic flora were reduced by 2.8 and 2.5 log at 5 and 60 minutes, respectively. The reduction in anaerobic flora was reported to be 1.7 log at 5 minutes and 1.2 log at 60 minutes.

Leaper, Lewis, and Speller (Ref. 18) compared the effectiveness of povidone-iodine impregnated drapes, povidone-iodine with a sterile drape, and conventional preoperative skin preparation with povidone-iodine for the reduction of skin bacteria. Forty-five subjects scheduled to undergo elective groin surgery were randomized to one of the three treatments. Impression plates and skin swabs were taken immediately before and after surgery, and swabs were taken before and after skin incision and closure. Conventional preoperative skin prepping with povidone-iodine produced the greatest reduction of the bacterial flora (240 colony counts to 34 colony counts, 2.3 $\log_{10}$ reduction).

Duignan and Lowe (Ref. 19) studied the effectiveness of povidone-iodine for reducing pathogenic bacteria in the vagina. A 1:10 solution of a povidone-iodine formulation containing 0.75 percent available free iodine was instilled into the vagina of 35 subjects and left in situ for 1 to 3 minutes. Aspirate cultures were taken from the vagina before and after preoperative disinfection and subcultured into thioglycollate broth containing neutralizers. Povidone-iodine removed 92 percent of the bacteroides species, anaerobic streptococci, gram negative bacilli, and *Streptococcus pyogenes* present prior to the preoperative disinfection.

A surveillance report (Ref. 1–C132) of hospital infections showed that the use of povidone-iodine in preparing patients for catheterization significantly reduced the rate of urinary tract infections. A 5-year study showed that the rate of urinary tract infections before October 1977 ranged from 5.2 percent to 11.5 percent (mean 7.6 percent), but beginning in October 1977 when povidone-iodine was the antiseptic solution in use, the rate ranged from 1.0 percent to 4.0 percent (mean 2.4 percent). At the 95 percent confidence level this is statistically significant. No method data accompanied the report except that the urethral meatus was cleansed with cotton dipped in the antiseptic solution before catheterization.

The agency believes that these studies and other published and publicly available medical and scientific data demonstrate that povidone-iodine is effective for use as a patient preoperative skin preparation. Although all of the trials were not done the same way, and thus they are not strictly comparable, the weight of the evidence shows that povidone-iodine is effective both as a preoperative skin preparation and surgical hand scrub, reducing the normal microbial flora by more than 90 percent and not showing any significant qualitative selection among the normal species found on the skin. In conclusion, povidone-iodine was effective against a wide spectrum of pathogenic and normal skin micro-organisms and maintained some suppressive effect on skin counts after the initial use.

In addition to the data reviewed supporting the safety and effectiveness of povidone-iodine for these professional uses, the agency classified povidone-iodine 5 to 10 percent as Category I as a first aid antiseptic in the tentative final monograph published in the **Federal Register** on July 22, 1991 (56 FR 33644). Accordingly, the agency is reclassifying povidone-iodine 5 to 10 percent from Category III to Category I for use as a topical antiseptic ingredient for use in surgical hand scrub, patient preoperative skin preparation, and antiseptic handwash or health-care personnel handwash drug products.

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18. Several comments objected to the agency's proposal that the professional labeling of povidone-iodine products containing molecules greater than 35,000 daltons should include warnings against parenteral use and against exposure of open surgical wounds or deep wounds to the product. (See comment 71, 43 FR 1210 at 1221.) Some of the comments contended that the Panel recommended such warnings because it felt there was widespread misuse (unapproved use) of povidone-iodine solution by surgeons bathing the peritoneal cavity with povidone-iodine during major surgery and then cleansing the area by rinsing. Another comment stated that because health-care personnel handwashes or surgical hand scrubs require a surfactant, such products so formulated would never be

considered for peritoneal lavage by surgeons. One comment argued that labeling to warn against parenteral use is clearly beyond the scope of the OTC drug review and FDA's regulatory authority. Another comment stated that it is unnecessary to establish an arbitrary molecular weight limit for povidone-iodine because no parenteral use of povidone-iodine is permitted in any of the approved labeling in the new drug applications for those products.

One comment stated that povidone-iodine is generally recognized as safe and effective for use in open wounds and a warning against such use would be contrary to clinical experience with this drug. In support of this position, the comment submitted a controlled study in which the surgical incisions of one group were irrigated before closure with 10 percent povidone-iodine solution, and the surgical incisions of the control group were irrigated before closure with saline solution (Ref. 1). The comment stated that the results of this study showed a significant decrease in infections when povidone-iodine was used, and there were no allergic, adverse, or other deleterious effects following this use of povidone-iodine.

In response to the Commissioner's recommendation for research data (43 FR 1210 at 1235), one comment submitted an extensive review of the extent of scavenging of residual povidone-iodine molecules by the reticuloendothelial system and possible lymph node involvement following use in the abdominal cavity or in large wounds (Ref. 2). The comment stated that, based on these data, povidone-iodine with medium molecular weights should not be limited to use on intact skin, nor should a warning be required. Another comment stated that the average molecular weight of povidone in the povidone-iodine that has been used exclusively in topical antimicrobial products for almost a quarter of a century is 37,900 daltons, and it presents no risk for any of the topical antimicrobial uses covered by the tentative final monograph.

The Panel recognized a relationship between molecular size and nodular lymphatic changes accompanying exposure to povidone-iodine, but made no decision on limiting the molecular size causing such pathology. (See 39 FR 33103 at 33130.) In the previous tentative final monograph, FDA evaluated data provided in a comment (Ref. 3) that contended there should be restrictions on the use of povidone-iodine according to molecular size. Published research cited in that comment indicated that povidone molecules larger than 40,000 daltons cannot be excreted by the kidneys, can cause nodules to appear in the lymphatic system, and may induce cosmetic deformities in the area of healing skin wounds. Based on expert opinion and the data provided in the comment (Ref. 3), the agency proposed that a molecular weight of 35,000 daltons be established as the safe upper limit for povidone-iodine products used parenterally. This calculation assumed that a povidone-iodine molecule with this molecular weight would be too large to pass through the kidney. (See comment 71, 43 FR 1210 at 1221.) FDA also noted its awareness of the inappropriate use of povidone-iodine products in open wounds and in the abdominal cavity during surgery. (See 43 FR 1235.) To promote proper use of povidone-iodine products, FDA proposed to recognize two categories of such products. Products with povidone-iodine molecular weights less than 35,000 daltons would be permitted for general use. Appropriate labeling would place each product in its proper category of use. The professional labeling of povidone-iodine products containing molecules greater than 35,000 daltons would also include warnings against parenteral use of, and exposure of open surgical wounds or deep wounds to, the product.

In this current tentative final monograph, the agency recognizes that the professional uses of povidone-iodine that are proposed as safe and effective are limited to a patient preoperative skin preparation, health-care personnel handwash, and surgical hand scrub. Further examination of the reference cited in the previous tentative final monograph (Ref. 3) reveals that the reported adverse effects were due to intravenous or parenteral use of povidone. Based on the more recent data and comments, the agency now believes that neither medium nor larger molecular weight povidone-iodine molecules present risks when limited to the topical uses included in this tentative final monograph. Larger molecules of povidone-iodine would not be absorbed if the drug is used for these professional uses in accordance with the monograph. Thus, there is no need for the professional labeling to limit the molecular weight of povidone-iodine products or to require special warnings related to the molecular weight of povidone-iodine. Accordingly, such labeling is not being included in this tentative final monograph.

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(2) Unpublished review of published and unpublished studies regarding lymph node changes and effect on the reticuloendothelial system resulting from use of PVP-iodine on intact skin, mucous membranes, and open wounds, Comment No. C111 (vol. III A), Docket No. 75N–0183, Dockets Management Branch.

(3) Unpublished review of published studies regarding intravenous or parenteral use of polyvinylpyrrolidone (PVP), Comment No. C40, Docket No. 75N–0183, Dockets Management Branch.

19. Several comments contended that there are numerous professional uses for povidone-iodine, particularly uses that involve medical devices, that were not discussed by the Panel or by the agency in the tentative final monograph. These professional uses include catheter care, ostomy hygiene, patient skin scrubbing prior to preoperative prepping, surgical site cleansing after stitching, mouth and throat swabbing, treatment of the skin before covering a fracture with a cast, antiseptic treatment of various scalp problems, and intravenous site preparation. One comment added that a pharmacist or other health professional may recommend the use of povidone-iodine as a douche, perianal wash, or whirlpool concentrate. The comments requested that special labeling be added to the monograph to cover all of these uses, but did not submit data regarding these uses.

One comment also provided professional labeling for povidone-iodine used for urinary or intravenous catheter care procedures. The suggested labeling included the following terms: "antiseptic," "germicide," "microbicidal," and "for hospital and professional use."

Several of the professional uses mentioned by the comments are not covered by this rulemaking, but they will be addressed under other OTC drug rulemakings. For example, the use of povidone-iodine for mouth and throat swabbing is included in the advance notice of proposed rulemaking for OTC oral health care drug products, published in the Federal Register of May 25, 1982 (47 FR 22760). The use of povidone-iodine for the treatment of scalp problems is addressed in the final rule for OTC dandruff, seborrheic dermatitis, and psoriasis drug products, published in the Federal Register of December 4, 1991 (56 FR 63554). The use of povidone-iodine as a douche is addressed in the advance notice of proposed rulemaking for OTC vaginal drug products, published in the Federal Register of October 13, 1983 (48 FR 46694).

The Advisory Review Panel on OTC Hemorrhoidal Drug Products stated that the inclusion of antiseptics in OTC anorectal drug products "is useful in concept," but "that proof of any significant clinical benefit of claimed antiseptic ingredients must be demonstrated in clinical trials" (45 FR 35576 at 35659). That Panel believed that, because of the large numbers of micro-organisms present in feces, there is little likelihood that effective antisepsis could be obtained in the anorectal area with antiseptics any more than with soap and water. Because no data were submitted on povidone-iodine as a perianal wash, the agency did not address this ingredient in the discussion of antiseptics in the tentative final monograph for OTC anorectal drug products when the agency evaluated the Panel's conclusions. Similarly, the ingredient was not included in the final rule for OTC anorectal drug products, published in the **Federal Register** of August 3, 1990 (55 FR 31766). Parties interested in this use of povidone-iodine can submit data and information as part of a citizen petition to amend the final rule for OTC anorectal drug products. (See 21 CFR 10.30.)

Several of the uses suggested by the comments are related to the general category of patient preoperative skin preparation that was discussed by the Panel. (See the **Federal Register** of September 13, 1974, 39 FR 33103 and 33114.) One example is the use "patient skin scrubbing prior to preoperative prepping." The agency believes that this use can more simply be described by the indication "for preparation of the skin prior to surgery," which is being proposed in § 333.460(b)(1)(i) of this tentative final monograph. Other uses are catheter care, ostomy hygiene, and intravenous site preparation. Some uses mentioned by the comments involve postoperative situations (surgical site cleansing after stitching) or do not even involve a surgical procedure (treatment of skin prior to covering a fracture with a cast or use as a whirlpool concentrate). The agency believes that instead of trying to identify in the product's labeling every possible situation where use of the product would reduce the risk of skin infection, this use of the product can best be described by the general indication "Helps to reduce bacteria that potentially can cause skin infection," which is being proposed in § 333.460(b)(1)(ii).

The agency has considered the term "for hospital and professional use only" suggested by one comment and finds it acceptable for professional labeling. (See section I.D., comment 8.) Likewise, the agency has no objection to terms such as "germicide," "germicidal," and "microbicidal" being used in professional labeling because health professionals understand the meaning of these terms. However, the agency does not believe there is a need to include in the monograph every one of these terms that might be used in the professional labeling of these products. These terms will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading.

J. Comments on Quaternary Ammonium Compounds

20. One comment requested that benzalkonium chloride be placed in Category I as a skin antiseptic, a patient preoperative skin preparation, and a skin wound protectant, in addition to its present Category I classification as a skin wound cleanser. In support of its request, the comment cited several surgery textbooks and other references that recommend use of benzalkonium chloride at concentrations ranging from 1:750 to 1:5,000 as a preoperative skin preparation, surgical scrub, skin antiseptic for venipuncture, and in urinary tract procedures, especially in catheterized patients (Ref. 1). The comment also submitted two studies on a product containing benzalkonium chloride at a concentration of 1:1,000: (1) An in vitro study to demonstrate that this product formulation acts as a physical chemical barrier against contamination by micro-organisms, and (2) a study on induced wounds on the arms of 10 healthy subjects to present evidence that this product is nonirritating and neither delays healing nor favors the growth of micro-organisms (Ref. 2).

The agency determined in the tentative final monograph for OTC first aid antiseptic drug products that the safe and effective concentration range for using benzalkonium chloride as a first aid antiseptic has been established as 0.1 percent to 0.13 percent. (See 56 FR 33644 and 33663.) Data submitted to the Antimicrobial I Panel and by the comment were sufficient to establish safety for products intended for short-term use, such as a first aid antiseptic drug product. The data submitted also support safety for use as a patient preoperative skin preparation, based on the short-term use of the drug for this purpose. However, the data reviewed by the Panel and supplemented by the comments to establish the efficacy of benzalkonium chloride for use as a topical antiseptic ingredient in patient preoperative skin preparations are not sufficient. The Antimicrobial I Panel placed this ingredient in Category III for this use. (See 39 FR 33103 and 33115.) The agency finds that the surgery textbooks and other references cited by the comment (Ref. 1) do not contain sufficient information about quantitative and qualitative changes in the microbial flora of the treated skin areas. Before benzalkonium chloride may be generally regarded as effective for use as a patient preoperative skin preparation, additional in vitro and in vivo effectiveness data are needed. The data should include results obtained from both in vitro and in vivo testing procedures as described for patient preoperative skin preparation drug products. (See section I.N., comment 28.)

Accordingly, benzalkonium chloride remains classified in Category III as a topical antiseptic ingredient for use as a patient preoperative skin preparation.

References

(1) Comment No. C116, Docket No. 75N–0183, Dockets Management Branch.

(a) Review of Scientific Literature on the Safety and Effectiveness of Zephiran Chlorideé as a "Skin Antiseptic" and "Patient Preoperative Skin Preparation" for the Preoperative Cleansing and Degerming Before Surgery and Use of Medical Devices.

(2) Unpublished Clinical Wound Healing Studies on Medi-Quiké, Comment No. SUP13, Docket No. 75N–0183, Dockets Management Branch.

(a) Statistical Analysis of Data from Efficacy Study of Medi-Quik as a Skin Wound Protectant in Humans.

(b) Studies on Medi-Quik as a Wound Protectant.

21. Two comments objected to the proposed warning statement in § 333.92(c)(6) for concentrated products containing quaternary ammonium compounds, which states, "Dilute with distilled water before use because acidic or hard water may render the product inactive." One comment contended that this proposed warning is prejudicial to the quaternary ammonium products that can act in acidic or hard water and noted that the existence of quaternary ammonium compounds that can act as antimicrobials in acidic or hard water was recognized in the tentative final monograph (43 FR 1210 at 1219). The comment recommended that the labeling of products containing quaternary ammonium compounds include a statement, based on appropriate laboratory tests, about the ability of the product to perform in acidic solutions and the amount of water hardness (described as parts per million (ppm) calcium carbonate) in which the product will continue to be effective.

The other comment stated that several concentrated quaternary ammonium compounds (e.g., 50 percent benzalkonium chloride, U.S.P.) registered with the Environmental Protection Agency (EPA) conform with the hard-water tolerance requirements and therefore can maintain activity at a water-hardness level of 600 ppm. The comment also stated that pH must be reduced below 3.5 before the effectiveness of quaternary ammonium compounds is decreased to any significant extent (Ref. 1). The comment concluded that, because normal potable water supplies do not approach these levels for either hardness or acidity, the requirement in proposed § 333.92(c)(6) for diluting only with distilled water is inappropriate and needless.

In the tentative final monograph, the agency acknowledged that hard water and acidity reduce the antimicrobial activity of quaternary ammonium compounds, but that there are some newer synthesized quaternary ammonium compounds that are not adversely affected by hard water and acidity (43 FR 1210 at 1218, 1219, and 1236). However, these newer quaternary ammonium compounds (e.g., a mixture of three benzalkonium halide compounds with varying chain lengths), while structurally related to benzalkonium chloride, benzethonium chloride, and methylbenzethonium chloride (the quaternary ammonium compounds which the Antimicrobial I Panel reviewed and which the agency proposed as Category III), were not reviewed or categorized by the Panel or the agency and are not included in this rulemaking. (See comment 58, 43 FR 1210 at 1219.) Further, the agency notes that the 50 percent quaternary ammonium concentrates that conform with EPA standards are intended for germicidal uses and not for the antiseptic uses that are being considered in this rulemaking.

The agency is aware that studies have shown that effects of acidic water on quaternary ammonium compounds occur only at dilutions containing less than the dosage concentration proposed in the tentative final monograph (Ref. 2). Higher concentrations minimize quaternary ammonium compound inactivation due to pH change (Ref. 3). However, it is well known that natural water supplies in different areas differ in acidity and hardness. As a precautionary measure, FDA believes that concentrates of the ingredients considered in this rulemaking should be diluted in distilled water by consumers and health-care professionals, because information about water pH or hardness in any given area is not usually known. Diluting the concentrated quaternary ammonium compound products addressed in this rulemaking with distilled water ensures that inactivating factors are not encountered. Therefore, the agency proposes to retain the warning statement, "Dilute with distilled water before use because acidic or hard water may render the product inactive," for diluting any Category I quaternary ammonium concentrate. However, because all the quaternary ammonium compounds remain in Category III at this time, the warning statement is not being included in this tentative final monograph.

References

(1) Lawrence, C. A., "Surface-Active Quaternary Ammonium Germicides," Academic Press Inc., New York, pp. 76–79, 1950.

(2) Kundsin, R. B., "Investigations on Dynamics of Bactericidal Action of Two Quaternary Ammonium Salts," *Archives of Surgery*, 81:789–797, 1950.

(3) Soike, K. F., D. D. Miller, and P. R. Elliker, "Effect of pH of Solution on Germicidal Activity of Quaternary Ammonium Compounds," *Journal of Dairy Science*, 35:764–771, 1952.

K. Comment on Sodium Oxychlorosene

22. One comment requested that sodium oxychlorosene be included in the monograph for use as a topical antiseptic for treating localized infections, to remove necrotic debris in massive infections, as a patient preoperative skin preparation and postoperative irrigant, and for the cleansing and disinfection of fistulae, sinus tracts, empyemas, and wounds. The comment included a number of references that recommended usage of sodium oxychlorosene (Ref. 1). The comment stated that "* * * the 25 years of marketing experience, the almost total absence of complaints, the number of published articles, the unusual spectrum of organisms reported on, all attest to the safety and efficacy of this product."

The agency has reviewed the data submitted and concludes that the available information does not contain any well-controlled clinical studies on the effectiveness of sodium oxychlorosene. In addition, no meaningful scientific information was presented in regard to safety. Clinical use for a period of years may provide corroborative evidence but is inadequate to support safe use. A good example is hexachlorophene; this drug had been used OTC for many years before more thorough safety studies in animals showed that the drug was not as safe as had been assumed. The agency concludes that the data are insufficient to demonstrate the safety and effectiveness of sodium oxychlorosene for OTC topical antiseptic use and therefore places this ingredient in Category III for both safety and effectiveness.

The agency's detailed evaluation of the data and information is on file in the Dockets Management Branch (Ref. 2).

References

(1) Published in vivo and in vitro studies, submitted by Guardian Chemical Corporation, Comment No. C126, Docket No. 75N–0183, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to R. Rubinger, Guardian Chemical Corporation, Comment No. ANS3, Docket No. 75N–0183, Dockets Management Branch.

L. Comments on Triclosan

23. A number of comments submitted data and information from microbiological, mutagenicity, metabolism, cross-sensitization, photosensitization, and drug experience studies on triclosan (Ref. 1). The comments stated that the data and information show that triclosan (up to 1.0 percent) is safe and effective and that triclosan should be placed in Category I for use in the categories that were defined in the previous tentative final monograph, i.e., skin antiseptic, skin wound cleanser, skin wound protectant, antimicrobial soap, health-care personnel handwash, patient preoperative skin preparations, and surgical hand scrub. In addition, one comment submitted information on triclosan (0.1 percent) for the treatment of diaper rash and on triclosan (0.1 percent) combined with benzocaine for the treatment of sunburn (Ref. 2).

One comment from the manufacturer of triclosan objected to the agency's expressed concern, as stated in the tentative final monograph (43 FR 1210 at 1231 and 1233), that there is a proliferation of products containing triclosan marketed to the American consumer (Ref. 3). The comment argued that the agency's concerns were without factual basis and submitted sales data, held confidential under 21 CFR 10.20(j)(2)(i)(*d*), showing that overall sales of triclosan in the U.S. have in fact decreased from 1973 to 1977 and that sales for use in bar soaps and deodorants have also declined from 1973 to 1977. The comment pointed out that it has exclusive U.S. patent rights for triclosan and that no license has been, or will be, granted under these patents. The comment added that to the best of its knowledge triclosan is not used in infant clothing, a use mentioned in the tentative final monograph at 43 FR 1231. The comment stated that if triclosan is placed in Category I for use

in antimicrobial soaps, it would limit sales of triclosan to OTC use in antimicrobial and deodorant soaps, underarm deodorants, and registered Environmental Protection Agency (EPA) pesticide products. In the future, sales might be extended to include approved new drug applications. The comment also pointed out that the statement at 43 FR 1233 about the EPA's Office of Special Pesticide Review preparing a report on the proliferation of triclosan-containing products is in error, and that the erroneous statement apparently resulted from a miscommunication between FDA and EPA staff. The comment concluded that the concerns about proliferation raised by the agency in the tentative final monograph should not prevent triclosan from being placed in Category I.

Another comment from the manufacturer of triclosan submitted validation reports and raw data from a 2-year chronic oral toxicity study in rats, and carcinogenicity and reproduction studies conducted in mice, rats, rabbits, and monkeys by Industrial Bio-Test Laboratories (IBT) (Refs. 4, 5, and 6) and asserted that its validation of the studies shows that triclosan is safe.

Several comments objected to the agency's restriction at 43 FR 1229 that antimicrobial soaps containing triclosan can only be formulated in a bar soap to be used with water (Ref. 1). The comments argued that such a restriction was not applied to the other Category III uses of triclosan, *i.e.*, skin antiseptic, skin wound cleanser, and skin wound protectant, and that such a restriction was not recommended by the Panel in the advance notice of proposed rulemaking. The comments suggested that the footnote under "antimicrobial soaps" limiting triclosan to bar soap was probably intended to apply to cloflucarban, which, like triclocarban, is known for its "physical and/or chemical incompatibility."

With regard to safety, the agency evaluated the validation reports to support long-term use of the ingredient (Refs. 4, 5, and 6) and advised the manufacturer of triclosan that the IBT studies were invalid because of numerous problems. The agency's detailed comments and evaluation on the data are on file in the Dockets Management Branch (Ref. 7).

The manufacturer subsequently stated its intent to no longer rely on the 2-year chronic oral toxicity IBT study (Ref. 8), and submitted a final report from a new 2-year chronic oral toxicity study in rats (Ref. 9). The agency has determined that the study data are unacceptable as the sole evidence of the safety of the long-term use of triclosan as a health-care personnel handwash or surgical handscrub based on the marginal survival of the animals in both the control and treated groups and uncertainties about the dose and study conduct. Therefore, data from another chronic exposure study are necessary to assess the safety of the long-term use of triclosan. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 10). A subsequent submission from the same manufacturer contained the final report of a two-generation study of the reproductive toxicity of triclosan in rats (Ref. 11). These data are currently being reviewed by the agency and will be discussed in the final rule for these drug products. Triclosan remains classified as Category III for safety for long-term use.

The agency concluded in the amended tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33665) that triclosan (in concentrations up to 1.0 percent) is safe for short term use as a first aid antiseptic (formerly designated as skin antiseptic, skin wound cleanser, and skin wound protectant). The data reviewed (Ref. 1) also support the safety of triclosan (up to 1.0 percent) for use as a patient preoperative skin preparation. However, with regard to safety for use as an antiseptic handwash or health-care personnel handwash and surgical hand scrub, triclosan remains classified in Category III for safety for long-term use, as stated above.

With regard to effectiveness, in the previous tentative final monograph the agency classified triclosan as Category II for use as a health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub because triclosan has limited activity against gram-negative bacteria. For example, triclosan is the subject of a patent (patent No. 3,616,256) for use in culture media for isolating *Pseudomonas*. Because human skin is regarded as a superb "culture medium," the possibility was raised (43 FR 1210 at 1232) that triclosan might selectively promote overgrowth of *Pseudomonas* on the hands of health-care personnel. Based upon data reviewed, the agency advised that in vitro data demonstrate that triclosan's antibacterial spectrum can be broadened, to be effective against *Pseudomonas* when triclosan is properly formulated with anionic surfactants to form a "synergistic mixture." Therefore, FDA reclassified triclosan (up to 1.0 percent, with the lower limit to be determined) from Category II to Category III for effectiveness. The agency further advised that additional studies are needed before triclosan can be generally recognized as effective for specific uses, *i.e.*, surgical hand scrub, health-care personnel handwash, patient preoperative skin preparation, and first aid uses (formerly designated as skin antiseptic, skin wound cleanser, and skin wound protectant). The agency's detailed comments are on file in the Dockets Management Branch (Ref. 12).

In response to the agency's comments (Ref. 12), the manufacturer of triclosan requested further guidance, and asserted, "The overall antimicrobial effectiveness of a topically applied product is a function of the total formulation rather than a single ingredient. Although it is impossible to anticipate and test all possible formulations, adequate in vivo evaluations of triclosan-containing formulations for specific end uses are available to fully justify Category I status for triclosan as an active ingredient in surgical hand scrubs, health-care personnel handwashes, and antimicrobial soaps." The comment submitted effectiveness data from four in vivo studies on formulations of triclosan (Ref. 13). These data included three previously unsubmitted studies (RDP/19/23 (June 24, 1981), RDP/19/21 (February 2, 1981), and CAB/AVD (February 2, 1982)), and one previously submitted study (66–D15–W221, OTC Volume 020038) that had been reviewed by the Panel (39 FR 33128). In study *RDP/19/23 (June 24, 1981)*, following modified glove juice test procedures, a test product (0.5 percent triclosan in 60 percent n-propyl alcohol) and a control (60 percent n-propyl alcohol) were compared for reduction of normal baseline flora and persistence of that reduction for 3 hours on the hands of 15 test subjects. The test product (0.5 percent triclosan in 60 percent n-propyl alcohol) and the control (60 percent n-propyl alcohol) immediately reduced approximately 99.5 percent of the baseline number of bacteria. After 3 hours, 0.5 percent triclosan in 60 percent n-propyl alcohol suppressed the baseline count better than the vehicle control; for example the test product allowed about a onefold increase in bacterial count within 3 hours, while the vehicle control (60 percent n-propyl alcohol) allowed an approximately twelvefold increase. Although the test used was not the glove juice test described in the antimicrobial tentative final monograph, alternative methods are acceptable, provided criteria meet those of the glove juice test procedures described in the guidelines. (See "Effectiveness Testing of Surgical Hand Scrub (Glove Juice Test)," 43 FR 1210 at

1242.) The agency has the following comments regarding the protocol for the study: only 15 subjects (an insufficient number) were tested; a baseline count from 3 samplings was not established before the test; the $\log_{10}$ reduction in bacteria from baseline was determined after 3 hours, but not after 6 hours; and the results of the test were not analyzed statistically.

In study *RDP/19/21 (February 2, 1981)*, 2 percent triclosan in a liquid soap vehicle reduced baseline counts of test bacteria *E. coli* ATCC 11229, *P. aeruginosa* ATCC 15442, and Staphylococcus species on the hands of human test subjects by 1 log greater than the water control after 2 minutes of handwashing. In study *CAB/AVD (February 2, 1982)*, triclosan (unknown concentrations) in a liquid soap formulation, compared to a vehicle control, maintained reduction of baseline counts (within 10, 30, 60, 90, and 120 minutes) after artificial contamination with *K. aerogenes*. In study *66–D15–W221 (in OTC Volume 020038)*, 0.5 percent, 1 percent, and 2 percent triclosan in Ivory^R soap was compared to Ivory^R soap without triclosan, as a control, to show reduction of baseline counts on the hands of five human test subjects after 5 days. Using the Quinn Split-Use Modification of the Price-Cade Method, increased skin-degerming activity was shown after 3 days of repeated (10) applications of triclosan as compared to the control. However, the number of test subjects (5) is not adequate to demonstrate general recognition of effectiveness. (See the "Modified Cade Procedure," 43 FR 1210 at 1243.)

The agency concludes that the data (Ref. 13) discussed above indicate that formulations of triclosan significantly reduce the baseline count of bacterial skin flora. However, before triclosan may be generally recognized as an effective health-care antiseptic for use in antiseptic handwash or health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub drug products, additional in vivo data, i.e., glove juice test data, are needed. The in vivo data should correlate with data obtained from in vitro studies. Because of the nature of the intended uses of health-care antiseptic drug products, the agency believes it is essential to assure the effectiveness of the active ingredient, triclosan, in final formulations. To demonstrate effectiveness in vitro, information is needed on the germicidal activity of the vehicle alone, so that the germicidal contribution of triclosan attributed to the total effectiveness of the finished formulation can be determined. (See section I.N., comment 28.)

Accordingly, triclosan (up to 1 percent, with the lower limit to be determined) is being classified as Category III for use in health-care antiseptic drug products as a patient preoperative skin preparation, antiseptic handwash or health-care personnel handwash, and surgical hand scrub. The agency's conclusions are summarized below:

Short-term use	Long-term (repeated/daily) uses
Patient Pre-operative Skin Preparation IIIE.	Antiseptic Handwash or Health-Care Personnel Handwash IIISE. Surgical Hand Scrub IIISE.

S=Safety.
E=Effectiveness.

The agency has communicated further with EPA and has ascertained that there is no specific report on the proliferation of triclosan (Ref. 14). Regarding exclusive patent rights, the agency advises that these are not among the determining criteria to establish general recognition of safety and effectiveness, and therefore cannot be used in the evaluation. However, having reviewed the new data along with the previously submitted data, the agency concludes that there is no proliferation problem with triclosan.

Finally, the agency did not intend to restrict formulations of triclosan to bar soap. The agency has reviewed the Panel's recommendations and the footnotes in the previous tentative final monograph (43 FR 1210 at 1229) and finds that triclosan under "antimicrobial soaps" was erroneously marked with the reference to the footnote "Category III only when formulated in a bar soap to be used with water."

The use of triclosan in products for the treatment of diaper rash was discussed in the tentative final monograph for antimicrobial diaper rash drug products published on June 20, 1990 (55 FR 25246 at 25277 to 25278). The use of triclosan in products for treating sunburn will be addressed in the **Federal Register** at a later date in another OTC drug rulemaking for drug products for this use.

References

(1) Comments No. CP1, SUP19, SUP23, C103, C109, SUP31, SUP39, and C134, Docket No. 75N–0183, Dockets Management Branch.

(2) Comment No. SUP20, Docket No. 75N–0183, Dockets Management Branch.

(3) Comment No. OB15, Docket No. 75N–0183, Dockets Management Branch.

(4) "Two Year Chronic Oral Toxicity Study With Fat 80′ 023/A in Albino Rats." Comment No. C109, vol. 1, appendix E, and Comment No. C139, vol. 1–8, Docket No. 75N–0183, Dockets Management Branch.

(5) "Eighteen Month Carcinogenicity Study with Fat 80′ 023/A in Albino Mice," Comment No. C109, vol. 3, appendix I, and Comment No. C139, vol. 9, Docket No. 75N–0183, Dockets Management Branch.

(6) "Three Phase Reproduction Study Albino Rats and Rabbits, Bacteriostat CH 3565," Comment No. C134, tab 7, and Comment No. C139, vol. 10–11, Docket No. 75N–0183, Dockets Management Branch.

(7) Letter from W. E. Gilbertson, FDA, to R. Bernegger, Ciba-Geigy Corp., coded LET28/ANS, Docket No. 75N–0183, Dockets Management Branch.

(8) Memorandum of meeting between representatives of Ciba-Geigy Corp. and FDA, Comment No. MM7, Docket No. 75N–0183, Dockets Management Branch.

(9) "FAT 80′ 023 2–Year Oral Administration in Rats," vol. XLI, XLII, and XLIII and "Determination of FAT 80′ 023 in Blood and Tissue Samples Taken During a Two-Year Chronic Oral Toxicity/Oncogenicity Study in Albino Rats," vol. XLIV, Comment No. RPT2, Docket No. 75N–0183, Dockets Management Branch.

(10) Letter from W. E. Gilbertson, FDA, to Per Stensby, Ciba-Geigy Corp., coded LET100, Docket No. 75N–0183, Dockets Management Branch.

(11) Comment No. RPT7, Docket No. 75N–0183, Dockets Management Branch.

(12) Letter from W. E. Gilbertson, FDA, to R. Bernegger, Ciba-Geigy Corp., coded LET34, Docket No. 75N–0183, Dockets Management Branch.

(13) Comments No. MM3 and C157, Docket No. 75N–0183, Dockets Management Branch.

(14) Letter from A. E. Castillo, EPA, to W. E. Gilbertson, FDA, coded LET33, Docket No 75N–0183, Dockets Management Branch.

M. Comments on Combinations of Active Ingredients

24. One comment stated that the Panel did not review safety and effectiveness data submitted to it on mercufenol chloride (orthohydroxyphenylmercuric chloride) 0.1 percent and secondary amyltricresols 0.1 percent as single ingredients and in combination for use as a patient preoperative skin preparation, skin antiseptic, and skin wound protectant (Ref. 1). The comment added that the agency did not discuss these ingredients alone or in combination in the previous tentative final monograph.

The comment asserted that secondary amyltricresols, mentioned in the previous tentative final monograph under phenol (43 FR 1210 at 1238), is not equivalent to phenol because of chemical differences and differing antimicrobial properties, formulation concentrations, and patterns of use. The comment requested the agency to make decisions on the safety and effectiveness of this ingredient when used alone, or

in combination, as a patient preoperative skin preparation, a skin antiseptic, or a skin wound protectant.

The agency has previously reviewed data for first aid antiseptic uses of 0.1 percent mercufenol chloride and 0.1 percent secondary amyltricresols and found the evidence insufficient to support their safety and effectiveness either as single ingredients or in combination (56 FR 33644 at 33668). Only safety data on animals were submitted by the comment (Ref. 1); in general, these studies were conducted on a very small number of animals, did not detail methodology, and did not adequately describe results (physical condition of the animals). The submitted in vitro studies also lack sufficient detail to establish the effectiveness of mercufenol chloride.

Secondary amyltricresols is a mixture of isomeric secondary amyltricresols, which are derivatives of phenol, and has pharmacological properties similar to phenol. The agency agrees with the comment that the mixture of secondary amyltricresols is not equivalent to phenol and should be categorized separately from phenol. The submitted safety data included a study by Broom (Ref. 2), who reported that amylmetacresol is relatively nontoxic and less toxic than hexylresorcinol in rats and mice.

No toxicity studies in humans were included in the information provided by the comment. However, in the tentative final monograph for OTC external analgesic drug products, published in the Federal Register of February 8, 1983 (48 FR 5852 at 5858), the agency proposed that metacresol up to a 3.6-percent concentration be considered safe when combined with camphor and that a 3-to-1 ratio of camphor to metacresol reduces the irritating properties of metacresol. Although cresols may cause some irritation when applied to minor wounds, the agency believes that secondary amyltricresols at the concentration requested (0.1 percent) would not present any safety concerns, particularly considering the short-term use of antiseptics as patient preoperative skin preparation drug products. The submitted data are, however, inadequate to establish the efficacy of secondary amyltricresols.

Data are also needed to determine the safety and effectiveness of the combination of mercufenol chloride and secondary amyltricresols. Only animal safety data are available, and these studies were limited to determinations of the minimum lethal dose by various routes of administration (Ref. 1). The submitted information on marketing history is not sufficient to provide general recognition of the safety of these ingredients. The data contained isolated reports of the combination of mercufenol chloride and secondary amyltricresols causing occasional skin irritation, such as burning and blistering (Ref. 1), adverse effects that need to be more fully studied.

Most of the effectiveness work on the combination of mercufenol chloride and secondary amyltricresols has been in vitro. The combination is reported to combine the antibacterial activity of the single ingredients, that is, mercufenol chloride which is primarily active against gram-negative organisms and secondary amyltricresols which is primarily active against gram-positive organisms (Ref. 3). One in vivo study on the effectiveness of the combination as a patient preoperative skin preparation showed a substantial reduction in the skin microflora (Ref. 4). However, because neutralizers were not used, bacteriocidal activity cannot be differentiated from residual bacteriostatic activity. In addition, the effect of the 50-percent alcohol in the alcohol-acetone vehicle was not taken into consideration. Alcohol, 60 to 95 percent, is in Category I for antiseptic health-care uses.

Under the agency's guidelines for OTC drug combination products (Ref. 5), Category I active ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in all respects and the combination is on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Accordingly, both mercufenol chloride and secondary amyltricresols and the combination of these ingredients are placed in Category III. The combination needs further testing of the combined ingredients compared to each individual active ingredient to establish effectiveness of the combination as a patient preoperative skin preparation.

The agency recommends that in vivo and in vitro effectiveness data be submitted. The data should be based on both in vitro and in vivo testing procedures as described for patient preoperative skin preparation drug products. (See section I.N., comment 28.)

References

(1) OTC Vol. 020093.

(2) Broom, W. A., "A Note on the Toxicity of Amyl-meta-cresol," *British Journal of Experimental Pathology*, 12:327–331, 1931.

(3) Dunn, C. G., "Germicidal Properties of Phenolic Compounds," *Industrial and Engineering Chemistry*, 28:609–612, 1936.

(4) Maddock, W. G., and L. K. Georg, "Further Experience with Mercresin," *American Journal of Surgery*, 45:72–75, 1939.

(5) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

25. One comment submitted data on a combination drug product containing calomel (mercurous chloride) 30 percent, oxyquinoline benzoate, and trolamine (triethanolamine) combined with fatty acids to form a soap compound, plus a phenol derivative that is currently marketed over-the-counter and is indicated for use in the prevention of venereal disease (syphilis and gonorrhea) (Ref. 1). The comment included a historical review and information on in vitro activity of one of the ingredients. According to the comment, in 1905 the discovery was made that calomel in combination with fats is an effective germicide against *Treponema pallidum* (*T. pallidum*), the causative organism of syphilis. Later, calomel was stated to be active against *Neisseria gonorrhoeae* (*N. gonorrhoeae*) (the causative organism of gonorrhea).

This combination of ingredients and the indication of prevention of syphilis and gonorrhea have not been reviewed by any OTC advisory review panel. However, because a claim is made indicating antimicrobial activity and the product contains calomel, which is already included in the rulemaking for OTC topical antimicrobial drug products, the agency believes it is appropriate to review this combination and labeling claim in this amended tentative final monograph.

The in vitro effectiveness test described in the comment (Ref. 1) is a zone of inhibition test comparing the germicidal activity of calomel, phenol, and organic silver salts against *S. aureus* as an indicator of activity against syphilis (*T. pallidum*) and gonorrhea (*N. gonorrhoeae*). According to the submission, the causative organisms are not viable in vitro and were not used in the testing. The agency points out that it is possible to isolate and subculture isolates of *N. gonorrhoeae* for in vitro antimicrobial testing (Ref. 2), but *T. pallidum* cannot be grown in vitro (Ref. 3). The agency does not consider the in vitro test against *S. aureus* to be adequate to support a claim of prevention of syphilis and gonorrhea.

In a separate rulemaking for mercury-containing drug products for topical antimicrobial use, calomel was reviewed by the Miscellaneous External Panel (47 FR 436 at 440). That Panel did note that calomel "has been used in the past by inunction (rubbing into the skin)

as a prophylactic against venereal disease * * *" but placed the ingredient in Category II because "calomel may be safe as a topical antimicrobial agent, but it is not effective for this purpose."

Although it is apparent that calomel 30 percent would be considered an active ingredient, it is not clear from the available information whether the other ingredients in the combination (oxyquinoline benzoate, trolamine, and phenol derivative) are also considered active ingredients, nor are the concentrations of these other ingredients stated in the submission and no data have been submitted to the OTC drug review on these ingredients in relation to the prevention of venereal disease. In the absence of any data, none of these ingredients are considered safe and effective for this use.

The comment did not submit any in vivo data from clinical studies to demonstrate that the combination of calomel, oxyquinoline benzoate, trolamine, and phenol derivative is safe and effective for use in the prevention of syphilis and gonorrhea. Preliminary in vitro testing against *N. gonorrhoeae* should be conducted before any human clinical trials are done. Then, favorable results from two well-controlled clinical studies in humans conducted by qualified investigators in two geographic locations (at least one should be within the United States of America) are needed before any drug product can be recognized to be safe and effective in preventing syphilis and gonorrhea. Interested individuals should consult with the agency before initiating any testing. In conclusion, the agency is proposing that this combination of ingredients indicated for the prevention of syphilis and gonorrhea be classified Category II in this amended tentative final monograph.

The agency's detailed comments and evaluation on the data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Comment No. C158, Docket No. 75N–0183, Dockets Management Branch.

(2) Morello, J. A., and M. Bohnhoff, "*Neisseria* and *Branhamella*," in "Manual of Clinical Microbiology," 3rd ed., edited by E. H. Lennette, *American Society for Microbiology*, Washington, pp. 111–122, 1980.

(3) Buchanan, R. E., and N. E. Gibbons, "Bergey's Manual of Determinative Bacteriology," 8th ed., Williams and Wilkins Co., Baltimore, p. 176, 1974.

(4) Letter from W. E. Gilbertson, FDA, to M. Lowenstein, The Sanitube Co., coded LET68, Docket No. 75N–0183, Dockets Management Branch.

N. Comments on Testing

26. Numerous comments addressed the agency's modifications in the Panel's proposed testing guidelines (43 FR 1210 at 1239 to 1240), the agency's statements on final formulation testing (43 FR 1211, 1224, and 1240), and specific protocols for upgrading an antimicrobial ingredient from Category III to Category I (43 FR 1242 to 1246). Stating that the testing guidelines were unclear in some places and pointing out inconsistencies between the guidelines and the agency's responses to comments at 43 FR 1211 and 1223 to 1227, a number of comments requested clarification or proposed modifications of a number of items in the guidelines.

Several comments requested specific information or submitted protocols for testing Category III ingredients. One comment requested that manufacturers be permitted to determine which protocol to follow to establish safety or effectiveness of an ingredient. A number of comments objected to the agency's consideration of the testing guidelines as final, and urged revisions in the guidelines for publication in the **Federal Register**.

The agency acknowledges that there were some inconsistencies in the testing guidelines for safety and effectiveness proposed in the previous tentative final rule. The agency does not consider the previous testing guidelines as final. The agency is clarifying in this amended tentative final monograph that all final formulations will be required to meet the specifications in the final monograph. As stated in section I.N., comment 28, the agency is proposing testing procedures in § 333.470 for evaluating the active ingredient in pure form as well as in the complete formulation. The agency recommends that manufacturers use these procedures for testing the final formulations of products intended for health-care antiseptic use. Manufacturers may propose other appropriate testing procedures subject to agency evaluation, as requested. The data from these tests are not required to be submitted to FDA by the manufacturer. However, the agency intends to use these procedures for any necessary compliance testing.

27. Two comments pointed out an apparent conflict in the agency's statements concerning safety factor calculations as follows: At 43 FR 1240, the agency concluded that a minimum of a 100-fold safety factor should apply to the exposure dose for ingredients labeled for repeated daily use; at 43 FR 1241, the agency stated that if the safety factor is extrapolated from an animal species to man, considering surface area, the highest no-effect dose should be used for the multiplier, and in the absence of complete data, a 100-fold safety factor should be applied when translating the animal highest no-effect dose to man; and at 43 FR 1213 (see comment 19), the agency stated that modifications of the safety factor will be allowed for specific ingredients where justified by risk-benefit considerations. One comment suggested that a safety factor of less than 100-fold be acceptable when scientific investigation of good quality shows that the test animals used in establishing the no-effect dose are similar to humans with respect to metabolism (biotransformation and pharmacokinetics) and/or tissue susceptibility. Another comment stated that a more reasoned and practical approach would be to require calculation of certain safety factors as recommended, and indicate in a general guideline that risk-benefit ratios based on these factors would determine the relative merits of the product.

The agency does not find any conflict in the various statements included in the previous tentative final monograph. The safety factor calculations were included merely as a general guideline. The agency's response to comment 19 at 43 FR 1213 indicated that the agency would retain a minimum of a 100-fold safety factor applied to the exposure dose for ingredients in products labeled for repeated daily use. However, the agency will consider modifications of the safety factor for specific ingredients where justified by risk-benefit considerations and where requests are based on submitted data. While the 100-fold safety factor was a general guideline in the previous tentative final monograph, the agency does not find a need to include a general guideline in this amended tentative final monograph.

28. Numerous comments requested clarification of the criteria required to establish effectiveness for each antimicrobial product class. One comment stated that the "Testing Guidelines" section seems to indicate that it may be necessary to determine the effect of the vehicle on the active ingredient. The comment contended that this provision is confusing because the preamble discussion in the tentative final monograph indicates that vehicle testing will not be necessary "* * * where adequate data are available on the active ingredients alone." (See 43 FR 1210 at 1224.) Another comment stated that the Cade handwashing test can only be conducted if the antimicrobial is placed in a vehicle and noted that the antimicrobial is never used by consumers in its raw form; therefore, efficacy testing on the raw antimicrobial

ingredient should not be required. A third comment stated that the overall antimicrobial effectiveness of a topically applied product is a function of the total formulation rather than a single ingredient. Another comment added that if an individual product formulation must be tested, and/or the testing of a product vehicle is considered essential, then such testing requirements must be specifically described. Citing the definition of an antiseptic in section 201(o) of the act (21 U.S.C. 321(o)), one comment asserted that the definition requires that the antimicrobial product kill or inhibit the growth of micro-organisms on the skin. The comment proposed that efficacy can be demonstrated by showing that the preparation produces a quantitative reduction in the levels of normal skin flora and/or inhibition of bacterial growth in vitro. Two comments pointed out that the "Modified Cade Procedure" handwashing test (43 FR 1210 at 1243) specifies a one-log reduction of bacteria, but the procedure fails to indicate how many uses or days of use of test product should produce the reduction. Other comments requested that no upper limit be set for bacterial hand counts, that the lower limit of 1.5×10^6 per hand be the only criteria for subject selection, and that minimal hand count reduction be defined in the test protocols for surgical hand scrub and health-care personnel handwash products. Another comment suggested that modification of the "Sampling technique and times" (paragraph 6) of the protocol "Effectiveness Testing of Surgical Hand Scrub (Glove Juice Test)" (43 FR 1243) was needed because the protocol did not indicate the volume of sampling solution but only stated that the volume * * * should be "kept constant" for all tests. The comment recommended that the agency specify a range of 50 to 100 mL of sampling solution in order to provide consistent and reproducible results.

The agency has carefully reviewed the comments, existing data, and other information, and is clarifying the effectiveness criteria for health-care antiseptics in this tentative final monograph.

In order for an antiseptic ingredient to be generally recognized as effective for use as an antiseptic handwash or health-care personnel handwash, patient preoperative skin preparation, and/or surgical hand scrub, it must have existing data from well designed clinical studies demonstrating effectiveness. The agency believes that it is important to correlate effectiveness data from clinical studies with effectiveness data from in vitro studies on the activity of the vehicle and active ingredient individually, so that the germicidal contribution of the antiseptic ingredient to the total formulation can be fully characterized. As stated in the testing guidelines in the previous tentative final monograph, at 43 FR 1240, "* * * there should be demonstration that the formulated product is better than the vehicle alone. Testing of the complete formulation of Category III ingredients * * * is necessary to judge the importance of the vehicle in the release of the active ingredient as well as the influence of formulation on aspects of effectiveness * * *." The agency believes that information on the in vitro activity of the active ingredient alone helps to characterize its antiseptic activity independent of formulation and helps to further define formulation effects on the antimicrobial ingredient. Therefore, the agency is proposing that in vitro studies of the antimicrobial activity of health-care antiseptic drug products covered by § 333.470(a)(1)(i) and (a)(1)(ii) be conducted on the active ingredient, the vehicle, and the final formulation. Manufacturers are to have such data in their files for products containing ingredients included in the monograph.

In this amended tentative final monograph, the agency is proposing that the in vitro antimicrobial activity of the antiseptic ingredient, the vehicle, and the formulated product be characterized by the determination of their antimicrobial spectrum and by minimal inhibitory concentration determinations performed against selected organisms using methodology established by the National Committee for Clinical Laboratories Standards (NCCLS) (Ref. 1). Because the principal intended use of these health-care antiseptic drug products is the prevention of nosocomial or hospital acquired infections, the agency concludes that these products should be able to demonstrate in vitro activity against a microbial spectrum that reflects this use. Since 1970, the National Nosocomial Infection Surveillance System (NNIS) has collected and analyzed data on nosocomial pathogens reported to the Centers for Disease Control by a number of hospitals who perform prospective surveillance on nosocomial infections. These data provide an indication of the most frequently occurring pathogens at four major sites of nosocomial infection—the urinary tract, surgical wounds, lungs (pneumonia), and bloodstream. The agency believes that health-care personnel handwash, surgical hand scrub, and patient preoperative skin preparations should be able to demonstrate in vitro effectiveness against these pathogens as well as the normal resident skin flora. Therefore, the agency is proposing that micro-organisms associated with the most commonly occurring nosocomial infections and those found most often in nosocomial infections of high risk patients as reported by the NNIS, for the period from January 1985 through August 1988 (Ref. 2), be included in the list of micro-organisms to be tested in § 333.470(a)(1)(ii). The agency further concludes that this proposed list identifies a broad spectrum of antimicrobial activity that is also appropriate for home use antiseptic handwash products.

The agency notes that neither filamentous dermatophytic fungi or viruses are included in the NNIS report. More recent studies (Refs. 3 and 4) have reported small numbers of nosocomial infections associated with both of these organisms. However, the new studies do not provide sufficient information to assess the relative importance of these organisms as a cause of nosocomial infection. Therefore, the agency is not proposing to include filamentous dermatophytic fungi in the list of micro-organisms to be tested, as proposed in the previous in vitro effectiveness testing guidelines (43 FR 1210 at 1241) and is continuing to propose that viruses also not be included. The agency recognizes that the list of organisms to be tested may need updating to assure that it remains reflective of current trends in the microbial etiology of nosocomial infections. The agency intends to update the list as new information becomes available. Further, the agency invites the submission of comments and specifically data on the role of other organisms, particularly viruses and filamentous dermatophytic fungi, in nosocomial infections.

In addition to the characterization of the in vitro spectrum of activity, the agency believes that information on how rapidly these antimicrobial drug products achieve their antimicrobial effect is necessary. As a means of indicating how quickly these products achieve their antimicrobial effect, the agency is proposing in vitro time-kill curves of the formulated drug product as part of the testing requirements. The agency acknowledges that there is currently no accepted or standardized method that may be used in conducting this type of study and invites the submission of proposed methods that may be considered as applicable to this test. In § 333.470(a)(1)(iv) of the proposed testing regulations, the agency provides guidance on the development

of such methods. However, any time-kill studies submitted to the agency are to be conducted on a 10-fold dilution of the formulated product against the ATCC strains identified in § 333.470(a)(1)(ii) of the proposed testing regulations and are to include enumeration at times at 0, 3, 6, 9, 12, 15, and 30 minutes.

With regard to proof of clinical effectiveness, the agency is proposing specific criteria for final formulations of antiseptic handwashes or health-care personnel handwashes, patient preoperative skin preparations, and surgical hand scrubs that are based on the recommendations of the Panel and agency experience in evaluating the effectiveness of these types of drug products, as follows.

For antiseptic handwash or health-care personnel handwash products, the agency is proposing the following criteria: (1) A 2-$\log_{10}$ reduction of the indicator organism on each hand within 5 minutes after the first wash and (2) a 3-$\log_{10}$ reduction in the indicator organism on each hand within 5 minutes after the tenth wash, when tested by a modification of the standard procedure for the evaluation of health-care personnel handwash formulations published by the American Society for Testing and Materials (ASTM) (Ref. 5).

For patient preoperative skin preparations, the agency is proposing the following criteria: (1) A 2-$\log_{10}$ reduction of the microbial flora per square centimeter of an abdominal test site, (2) a 3-$\log_{10}$ reduction of the microbial flora per square centimeter of a groin test site within 10 minutes from a matched control area, and (3) the suppression of bacterial growth below baseline for 6 hours, when tested by a modification of the standard procedure for the evaluation of patient preoperative skin preparations published by the ASTM (Ref. 6). The agency believes that the revised effectiveness criteria more closely reflect the conditions of product use, *i.e.*, on a number of different body sites, each supporting different numbers of resident skin flora. In addition, although persistence of effect was not recommended by the Panel as a requirement for these drug products, the agency believes that persistence of antimicrobial effect would suppress the growth of residual skin flora not removed by preoperative prepping as well as transient micro-organisms inadvertently added to the operative field during the course of surgery and reduce the risk of surgical wound infection. Based on the proposed effectiveness criteria for this product class, the agency is proposing a revised definition of a patient preoperative skin preparation drug product in § 333.403(c)(2) of this amended tentative final monograph as follows: "A fast-acting broad-spectrum persistent antiseptic-containing preparation that significantly reduces the number of micro-organisms on intact skin."

As discussed in section I.E., comment 10, the agency is proposing the indication "for the preparation of the skin prior to an injection" for OTC alcohol and isopropyl alcohol drug products. The agency is further proposing that products labeled for such use demonstrate effectiveness by testing according to the same procedure used to demonstrate the effectiveness of patient preoperative skin preparation drug products not labeled for this use. Based on this intended use of alcohol drug products, the agency is proposing a 1-$\log_{10}$ reduction in the microbial flora per square centimeter of a dry skin test site within 30 seconds of product use as the effectiveness criteria for these products.

For surgical hand scrub products, the agency is proposing the following criteria: (1) A 1-$\log_{10}$ reduction of the microbial flora of each hand from the baseline count within 1 minute, (2) suppression of bacterial growth on each hand below baseline for 6 hours on the first day, (3) a 2-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the second day, and (4) a 3-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the fifth day, when tested by a modification of the standard procedure for the evaluation of surgical hand scrub products published by the ASTM (Ref. 7).

Based on glove juice test data for surgical hand scrub use of povidone-iodine (section I.I., comment 17), alcohol (section I.E., comment 10), chloroxylenol (section I.G., comment 12), and triclosan (section I.L., comment 23), the agency concludes that formulated products containing certain ingredients, *i.e.*, chloroxylenol and triclosan, are substantive in their action and do not produce a high (1-$\log^{10}$) initial reduction, but after repeated use for up to 5 days do reduce the baseline count and suppress the count in the user's glove. In a separate final rule, the agency stated that any product indicated for use as a surgical scrub should meet a standard for initial reduction. A one-log reduction was found acceptable as the minimal level of reduction suitable for a surgical scrub in a handwashing test. (See "New Drugs Containing Hexachlorophene," published in the Federal Register of December 20, 1977; 42 FR 63771.)

In that same final rule, the agency acknowledged that hexachlorophene containing surgical scrub drug products are substantive in their action and do not produce an initial high reduction but with repeated use are effective in reducing the resident skin flora and suppressing bacterial growth in the user's glove for up to 6 hours. Based on a lack of available products capable of producing both an initial high reduction in the resident skin flora and a prolonged microbial suppression marketed at the time of the agency's action on the ingredient in 1972, the agency agreed with the recommendations of its Antimicrobial I Panel and concluded that the ingredient should continue to be marketed for use as a surgical scrub and for handwashing as part of patient care. The agency stated its intention to reconsider its criteria for evaluating such products in light of risk-benefit judgments as new products containing both attributes become available (42 FR 63771).

Since that final rule was issued in 1977, data have been submitted to the agency demonstrating the effectiveness of surgical hand scrub formulations capable of producing an initial 1-$\log_{10}$ reduction and a suppression of microbial growth in the wearer's glove for up to 6 hours. (See section I.E., comment 10 on alcohol and section I.I., comment 17 on povidone-iodine.) The agency notes that the persistence of the antimicrobial effect demonstrated by an alcohol-containing surgical hand scrub formulation was provided by a preservative agent in the vehicle. Based on the new data, the agency has concerns about the risk associated with the initial use of substantive surgical hand scrub formulations, and with the use of these formulations after extended lapses in their routine use. Therefore, the agency is proposing that all surgical hand scrub formulations must demonstrate an initial one-log reduction in the bacterial flora. The agency invites comment on the use of substantive antimicrobials in health-care antiseptic drug products. Based on the revised effectiveness criterion for these drug products, the agency is proposing a revised definition of a surgical hand scrub drug product in § 333.403(c)(3) as follows: "An antiseptic containing preparation that significantly reduces the number of micro-organisms on intact skin; it is broad spectrum, fast acting, and persistent."

The agency believes that the modified ASTM procedures for the testing of health-care or antiseptic handwashes, surgical hand scrubs, and patient preoperative skin preps being proposed for inclusion in the testing requirements

provide protocols that are appropriate for the final formulation testing of these drug products. The proposed protocols describe, in detail, study conditions and materials to be used and address the concerns raised by the comments. For instance, the proposed protocol for the testing of surgical hand scrub products includes a baseline criterion for subject selection of equal to, or greater than, 1.5×10^5 bacteria per hand and specifies that a 50 to 100 mL volume of sampling is to be used. The proposed protocols also specify requirements for a number of areas not addressed by the testing guidelines proposed in the previous tentative final monograph. For example, they address statistical aspects of study design and data analysis, and the use of neutralizers. A positive control is included in the protocols as a means of validating the testing procedure, equipment, and facilities. The agency believes that the proposed protocols for the testing of these products provide a consistent approach to the effectiveness testing of health-care personnel handwashes, surgical hand scrubs, and patient preoperative skin preparations. The agency is incorporating the above criteria and testing requirements in proposed § 333.470 of this tentative final monograph and invites specific comment on them at this time. After reviewing any submitted comments or data, the agency may revise the testing requirements and procedures prior to establishing a final monograph. The agency also recognizes that the test procedures may need to be revised periodically to reflect new information and newer techniques that are developed and proven adequate.

References

(1) National Committee for Clinical Laboratory Standards, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—2d ed.; Approved Standard," NCCLS Document M7–A2, 10:8, 1990.

(2) Horan, T. *et al.*, "Pathogens Causing Nosocomial Infections," *The Antimicrobic Newsletter*, 5:65–67, 1988.

(3) Andersen, L. J., "Major Trends in Nosocomial Viral Infections," *The American Journal of Medicine*, 91:107S–111S, 1991.

(4) Jarvis, W. R. *et al.*, "Nosocomial Outbreaks: The Centers for Disease Control's Hospital Infections Program Experience," *The American Journal of Medicine*, 91:101S–106S, 1991.

(5) American Society for Testing and Materials, "Standard Test Method for Evaluation of Health Care Personnel Handwash Formulation, Designation E 1174," in "The Annual Book of ASTM Standards," vol. 11.04, American Society for Testing and Materials, Philadelphia, pp. 209–212, 1987.

(6) American Society for Testing and Materials, "Standard Test Method for Evaluation of a Preoperative Skin Preparation, Designation E 1173," in "The Annual Book of ASTM Standards," vol. 11.04, American Society for Testing and Materials, Philadelphia, pp. 205–208, 1987.

(7) American Society for Testing and Materials, "Standard Test Method for Evaluation of Surgical Hand Scrub Formulation, Designation 1115," in "The Annual Book of ASTM Standards," vol. 11.04, American Society for Testing and Materials, Philadelphia, pp. 201–204, 1986.

II. The Agency's Amended Tentative Final Monograph

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. Summary of Ingredient Categories

The agency has carefully reviewed the claimed active ingredients submitted to this administrative record (Docket No. 75N–0183), which includes the following: the advance notice of proposed rulemaking (39 FR 33103) and previous tentative final monograph (43 FR 1210) for OTC topical antimicrobial drug products, the advance notice of proposed rulemaking for OTC topical alcohol drug products (47 FR 22324), and the advance notice of proposed rulemaking for OTC topical mercury-containing drug products (47 FR 436). Based upon the available information, including clinical and marketing history, as well as the recommendations of the Miscellaneous External Panel, the agency is proposing a tentative classification for OTC health-care antiseptic active ingredients.

Many of the ingredients included in the tabulation below are in Category II and Category III because of no data or a lack of data on use as a health-care antiseptic. However, all the ingredients have been included as a convenience to the reader. The agency specifically invites comment and additional data on these ingredients.

The advance notice of proposed rulemaking for alcohol drug products for topical antimicrobial OTC human use (47 FR 22324, May 21, 1982) is being incorporated into this amended tentative final monograph. In that proposed monograph, the Miscellaneous External Panel recommended that alcohol 60 to 95 percent by volume in an aqueous solution denatured according to Bureau of Alcohol, Tobacco, and Firearms regulations at 27 CFR part 21 and isopropyl alcohol 50 to 91.3 percent by volume in an aqueous solution be classified as Category I for topical antimicrobial use. The following indications were proposed:

(1) "For first aid use to decrease germs in minor cuts and scrapes."

(2) "To decrease germs on the skin prior to removing a splinter or other foreign object."

(3) "For preparation of the skin prior to an injection." (See the advance notice of proposed rulemaking for OTC alcohol drug products for topical antimicrobial use, in the **Federal Register** of May 21, 1982, 47 FR 22324.)

Based upon submitted data and the conclusions of the Miscellaneous External Panel, the agency is including alcohol as a Category I surgical hand scrub, patient preoperative skin preparation, and antiseptic handwash or health-care personnel handwash (see section I.E., comment 10). While no comments submitted data on health-care uses of isopropyl alcohol, the agency notes that one comment (Ref. 1) from a manufacturer requested that the OTC alcohol drug products monograph provide the labeling indication, "antibacterial handwash." The same manufacturer provided a submission (Ref. 2) to the Miscellaneous External Panel on a combination product containing isopropyl alcohol 50 percent and oxyquinoline sulfate 0.125 percent for use as a germicidal-fungicidal wash. However, the Panel disbanded before it was able to review the submission, which contained labeling for a currently marketed product and in vitro studies of the product's bacteriocidal activity. No in vivo effectiveness data were submitted for the use of isopropyl alcohol as an antiseptic handwash or health-care personnel handwash, patient preoperative skin preparation, or surgical hand scrub.

Based on the lack of data for the use of isopropyl alcohol as an antiseptic handwash or health-care personnel handwash and surgical hand scrub, the agency is placing the ingredient in Category III for these uses. The agency invites data on these uses of isopropyl alcohol. As discussed in section I.E., comment 10, the agency is including the Panel's recommended indication "for the preparation of the skin prior to an injection" as an additional Category I indication for patient preoperative skin preparations containing alcohol. Based on the Panel's recommendations, the agency is also proposing isopropyl alcohol as a Category I patient preoperative skin preparation for this indication. However, based on the lack of data on the use of isopropyl alcohol for more general patient preoperative skin preparation use, the agency is not proposing isopropyl alcohol as Category I for the other patient preoperative skin preparation indications included in § 333.460(b)(1), *i.e.*, "for the preparation of the skin prior to surgery" and "helps

to reduce bacteria that potentially can cause skin infection."

The agency has evaluated standard textbooks and published data on the effectiveness of isopropyl alcohol used topically on the area prior to an injection (Refs. 3, 4, and 5). The minimum effective concentration of isopropyl alcohol for this use is 70 percent. Further, the agency is not aware of any information concerning the use of isopropyl alcohol below 70 percent for this indication. Therefore, the agency is proposing to include isopropyl alcohol 70 to 91.3 percent in Category I for use as a patient preoperative skin preparation for the limited indication "for the preparation of the skin prior to an injection".

The Miscellaneous External Panel recommended that drug products containing alcohol and isopropyl alcohol bear the following warning: "Flammable, keep away from fire or flame," (47 FR 22324 at 22330). The agency concurs with the Panel's recommended warning and is proposing this warning in § 333.450(c)(4) of this tentative final monograph. In order to ensure the warning's prominence, the agency is further proposing that it appear in boldface type and as the first warning immediately following the heading "WARNINGS".

The agency is aware of ten reports (Refs. 6 and 7) of first and second degree burns occurring in patients undergoing electrocautery procedures. The burns were caused by the ignition of the isopropyl alcohol in patient preoperative skin preparations containing chlorhexidine gluconate or povidone-iodine in 70 percent isopropyl alcohol. The reports indicate that these incidents have occurred despite the presence of detailed warnings in the products' labeling cautioning that the products are flammable until dry and should not be allowed to pool on body surfaces or should not be used in conjunction with electrocautery procedures until dry (Refs. 8 and 9). Based on these reports, the agency tentatively concludes that patient preoperative skin preparations containing isopropyl alcohol in concentrations of 70 percent or more cannot be adequately labeled to allow the safe use of these drug products in conjunction with electrocautery procedures. Therefore, the agency is proposing that patient preoperative skin preparations containing isopropyl alcohol in concentrations of 70 percent or more bear the following label warning: "Do not use with electrocautery procedures." The agency is further proposing that the proposed warning immediately follow the flammable warning being proposed in § 333.450(c)(4).

The agency is not currently aware of any similar incidence occurring with other nonemollient patient preoperative skin preparations containing alcohol in similar concentrations. Therefore, at this time the agency is not proposing that patient preoperative skin preparations containing alcohol identified in § 333.412(a) bear a warning concerning the use of these products in conjunction with electrocautery procedures. However, the agency will consider extending the warning to patient preoperative skin preparations containing alcohol if new information indicates that this is necessary. The agency invites specific comment and data on the safety of both alcohol and isopropyl alcohol containing patient preoperative skin preparations in conjunction with electrocautery procedures.

References

(1) Comment No. C00148, Docket No. 75N–0183, Dockets Management Branch.

(2) OTC Vol. 160251.

(3) Lee, S., I. Schoen, and A. Malkin, "Comparison of Use of Alcohol with that of Iodine for Skin Antisepsis in Obtaining Blood Cultures," *American Journal of Clinical Pathology*, 47:646–648, 1967.

(4) Harvey, S.C., "Isopropanol," in "The Pharmacological Basis of Therapeutics," 7th ed., Macmillan Publishing Co., New York, p. 962, 1985.

(5) Harvey, S.C., "Isopropyl Alcohol," in "Remington's Pharmaceutical Sciences," 16th ed., Mack Publishing Co., Easton, PA, pp. 1103–1104, 1980.

(6) Drug Experience Reports No. 184970, 190547, 190548, 190549, 807471, and 851772 in OTC Vol. 230001, Docket No. 75N–183H, Dockets Management Branch.

(7) Transcripts of consumer complaints regarding DuraPrep™ Surgical Solution dated January 31, 1991, April 8, 1992, and April 9, 1992 in OTC Vol. 230001, Docket No. 75N–183H, Dockets Management Branch.

(8) Labeling for DuraPrep Surgical Solution, in OTC Vol. 230001, Docket No. 75N–183H, Dockets Management Branch.

(9) Physicians' Desk Reference, 38th ed., Medical Economics Company, Oradell, NJ, p. 1956, 1984.

The Panel also stated that benzyl alcohol and chlorobutanol were safe, but recommended that the ingredients be categorized as Category II for effectiveness. However, in the first aid antiseptic segment of this rulemaking these alcohol ingredients were reclassified from Category II to Category III for effectiveness as first aid antiseptic ingredients. (See 56 FR 33644 at 33673.) Because no comments, data, or information were received, and because the agency is not aware of any health-care antiseptic uses for these ingredients, benzyl alcohol and chlorobutanol are not being classified in this rulemaking for health-care antiseptic drug products.

The agency published an advance notice of proposed rulemaking for mercury-containing drug products on January 5, 1982 (47 FR 436). That notice, based upon the recommendations of the Miscellaneous External Panel, proposed to classify OTC mercury-containing drug products for topical antimicrobial use as not generally recognized as safe and effective and as being misbranded. The agency received no comments. The Panel classified the mercurial ingredients, as a group, in Category II; some for lack of safety, some for lack of efficacy, and others due to a lack of both safety and efficacy. However, in the first aid antiseptic segment of this amended tentative final monograph, several mercury-containing OTC topical antimicrobials have been reclassified from Category II to Category III for effectiveness. Mercurial ingredients placed in Category II for safety were not reclassified. The ingredients reclassified are calomel, merbromin, mercufenol chloride, and phenylmercuric nitrate. This change was made in keeping with the revised effectiveness criteria for the drug product category "first aid antiseptic," which were not available at the time the Miscellaneous External Panel evaluated the effectiveness of mercurial ingredients. (See 56 FR 33644 at 33672.) The agency is unaware of any clinical data or marketing history for the use of mercury-containing drug products as health-care antiseptics. Consequently, these drugs have not been classified as health-care antiseptics. In addition, the agency has reviewed submitted data on two combinations containing mercurial ingredients and proposes a Category II classification for these combinations. (See section I.M., comments 24 and 25.)

In the previous tentative final monograph, the agency concluded that cloflucarban and triclocarban are not generally recognized as safe and effective for use as a patient preoperative skin preparation, surgical hand scrub, and health-care personnel handwash. The Panel reviewed safety and effectiveness data on these ingredients formulated as a bar soap and classified them in Category III as a health-care personnel handwash when formulated as a bar soap (39 FR 33103 at 33124 and 33126). No safety and effectiveness data for the use of clofucarban in the other health-care antiseptic drug product classes were submitted to the OTC drug review; no data were reviewed by the Panel; and no data were received by the agency.

Cloflucarban is therefore considered to be outside this monograph except as a health-care personnel handwash (formulated as a bar soap). Accordingly, cloflucarban remains Category II as a health-care antiseptic for use as a patient preoperative skin preparation and surgical scrub and Category III as an antiseptic handwash or health-care personnel handwash.

Additional safety data and information were submitted to the agency on triclocarban formulated as a soap. As discussed in the segment of this rulemaking covering first aid antiseptics (56 FR 33644 at 33664), the agency has reviewed a chronic toxicity study and other information and determined that triclocarban can be recognized as safe for OTC daily topical use in a concentration of 1.5 percent. However, no effectiveness data were submitted for any health-care antiseptic uses of this ingredient and the agency is classifying triclocarban in Category III as an antiseptic handwash or health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub. In the previous tentative final monograph, the agency placed the combination of cloflucarban and triclocarban in Category III (43 FR 1210 at 1230) to be "used in antimicrobial soap * * *". No additional data were submitted on this combination. Therefore, the combination of cloflucarban and triclocarban remains in Category III for antiseptic handwash or health-care personnel handwash uses.

Based upon the Panel's recommendations on phenol, in the previous tentative final monograph, the agency classified phenol less than 1.5 percent as Category III and phenol greater than 1.5 percent as Category II for use as a health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub (43 FR 1227 and 1229). Hexylresorcinol was also classified in Category III for these uses in the previous tentative final monograph (43 FR 1229). No additional data were submitted on health-care antiseptic uses of phenol and hexylresorcinol and their classifications are unchanged in this amended tentative final monograph. In the previous tentative final monograph, the agency classified triple dye (a combination of gentian violet, brilliant green, and proflavine hemisulfate) in Category II as a health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub based on a lack of safety data (43 FR 1239). No additional data have been submitted and the ingredient remains in Category II for health-care antiseptic uses.

In comment 85 of the previous tentative final monograph (43 FR 1223), the agency deferred classification of several ingredients to the Miscellaneous External Panel. All of the ingredients have been classified with the exception of methyl alcohol and gentian violet 1 and 2 percent solutions. The Miscellaneous External Panel at its 38th meeting placed methyl alcohol in Category II as an OTC topical antimicrobial ingredient for both safety and effectiveness (Ref. 1). However, this classification was not included in the advance notice of proposed rulemaking for OTC alcohol drug products. The agency agrees with this classification. Further, the agency is not aware of any use of methyl alcohol in OTC drug products, except as a denaturant. Gentian violet was reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products and placed in Category III based on the lack of effectiveness data for use as a topical antimicrobial on the mucous membranes of the mouth. The agency is not aware of any data on the use of gentian violet as a health-care antiseptic and places this ingredient in Category II for this use.

Reference

(1) Transcript of the Proceedings of the 39th Meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products, April 20, 1980, pp. 121–123.

Fluorosalan was not classified as an OTC topical antimicrobial ingredient in the previous tentative final monograph because the agency stated that final regulatory action had been taken against "* * * the halogenated salicylanilides, particularly * * * fluorosalan (21 CFR 310.508) * * *" (43 FR 1210 at 1227). Although no comments were received, the agency notes that fluorosalan was not addressed in the final rule for halogenated salicylanilides (21 CFR 310.508), published in the **Federal Register** of October 30, 1975 (40 FR 5027). In reviewing the Antimicrobial I Panel's recommendations, the agency has determined that the Panel did not intend to include fluorosalan in the group of halogenated salicylanilides which it recommended be handled more expeditiously by the agency in a separate **Federal Register** notice. (See the notice of proposed rulemaking for certain halogenated salicylanilides as active or inactive ingredients in drug and cosmetic products (September 13, 1974, 39 FR 33102) and the advance notice of proposed rulemaking for OTC topical antimicrobial drug products (September 13, 1974, 39 FR 33103 at 33120).) The agency affirms the recommendation of the Antimicrobial I Panel (39 FR 33121) that fluorosalan be classified as Category II for use in antiseptic handwash, health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub drug products.

The following charts are included as a summary of the categorization of health-care antiseptic active ingredients proposed by the agency.

TOPICAL ANTIMICROBIAL INGREDIENTS [1] SUMMARY OF HEALTH-CARE ANTISEPTIC ACTIVE INGREDIENTS

Active ingredient	Patient preoperative skin preparation	Antiseptic handwash or health-care personnel handwash	Surgical hand scrub
Alcohol 60 to 95 percent [2]	I	I	I
Benzalkonium chloride	IIIE	IIISE [4]	IIISE
Benzethonium chloride	IIIE	IIISE	IIISE
Chlorhexidine gluconate [2]	([5])	([5])	([5])
Chloroxylenol	IIIE	IIISE	IIISE
Cloflucarban	II	IIISE	II
Fluorosalan	II	II	II
Hexachlorophene	II	II	II
Hexyiresorcinol	IIIE	IIIE	IIIE
Iodine Active Ingredients:			
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate) [2].	NA	IIIE	IIIE
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol) ..	IIIE	IIIE	IIIE
Iodine tincture U.S.P	I	NA	NA

TOPICAL ANTIMICROBIAL INGREDIENTS [1] SUMMARY OF HEALTH-CARE ANTISEPTIC ACTIVE INGREDIENTS—Continued

Active Ingredient	Patient preoperative skin preparation	Antiseptic handwash or health-care personnel handwash	Surgical hand scrub
Iodine topical solution U.S.P	I	NA	NA
Nonylphenoxypoly (ethyleneoxy) ethanoliodine	IIIE	IIIE	IIIE
Poloxamer-iodine complex	IIIE	IIIE	IIIE
Povidone-iodine 5 to 10 percent	I	I	I
Undecoylium chloride iodine complex	IIIE	IIIE	IIIE
Isopropyl alcohol 70–91.3 percent [2]	I	IIIE	IIIE
Mercufenol chloride [2]	IIIE	NA	NA
Methylbenzethonium chloride	IIIE	IIISE	IIISE
Phenol (less than 1.5 percent)	IIIE	IIISE	IIISE
Phenol (greater than 1.5 percent)	II	II	II
Secondary amyltricresols [2]	IIISE	IIIE	IIIE
Sodium oxychlorosene [2]	IIISE	IIISE	IIISE
Tribromsalan [3]	II	II	II
Triclocarban	IIIE	IIIE	IIIE
Triclosan	IIIE	IIISE	IIISE
Combinations			
Calomel, oxyquinoline benzoate, triethanolamine, and phenol derivative [2].	II	NA	NA
Mercufenol chloride and secondary amyltricresols in 50 percent alcohol [2].	IIISE	NA	NA
Triple Dye	II	NA	NA

[1]—All ingredients (unless otherwise noted) in Antimicrobial I Drug Products Advance Notice of Proposed Rulemaking (39 FR 33103) and Tentative Final Monograph (47 FR 1210).
[2]—Not categorized in previous tentative final monograph, but categorized in this amended tentative final monograph.
NA=Not Applicable because not evaluated for this use.
[3]—Categorized in Antimicrobial I Drug Products Advance Notice of Proposed Rulemaking (39 FR 33103) and in Certain Halogenated Salicylanilides as Active or Inactive Ingredients in Drug and Cosmetic Products (40 FR 50527).
[4]—S=safety; E=effectiveness
[5]—Determined by the agency to be a "new drug".

SUMMARY OF TOPICAL ANTIMICROBIAL ACTIVE INGREDIENTS NOT ADDRESSED IN THIS RULEMAKING

Ingredients not classified as health-care antiseptic ingredients but generally recognized as safe and effective for OTC first aid use within the established concentration(s) (see 56 FR 33644).

Single ingredients

Alcohol 48 to 59 percent
Hydrogen peroxide topical solution U.S.P.
Isopropyl alcohol 50 to 69 percent

Combinations

Eucalyptol 0.091 percent, menthol 0.042 percent, methyl salicylate 0.055 percent, and thymol 0.063 percent in 26.9 percent alcohol.

Complexes

Camphorated metacresol (3 to 10.8 percent camphor and 1 to 3.6 percent metacresol) in a ratio of 3:1
Camphorated phenol (10.8 percent camphor and 4.7 percent phenol) in light mineral oil, U.S.P. vehicle

Ingredients not classified as Category I as a health-care antiseptic because the agency is not aware of any health-care antiseptic uses for these ingredients.

Single ingredients

Ammoniated mercury
Benzyl alcohol
Calomel (Mercurous chloride)
Chlorobutanol
Gentian violet
Merbromin
Mercuric chloride (Mercury chloride)
Mercuric oxide, yellow
Mercuric salicylate
Mercuric sulfide, red
Mercury
Mercury oleate
Mercury sulfide
Methyl alcohol
Nitromersol

SUMMARY OF TOPICAL ANTIMICROBIAL ACTIVE INGREDIENTS NOT ADDRESSED IN THIS RULEMAKING—Continued

Para-chloromercuriphenol
Phenylmercuric nitrate
Thimerosal
Vitromersol
Zyloxin
Combinations and/or Complexes
None

2. Testing of Category II and Category III Conditions

Required testing procedures for evaluating the effectiveness of the complete formulation of a health-care antiseptic drug product are included in proposed § 333.470. These effectiveness testing procedures can also be used to demonstrate the effectiveness of active ingredients not in a final formulation. Suggested safety testing is described in the previous tentative final monograph. (See 43 FR 1210 at 1240 to 1242.)

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any health-care antiseptic ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Conclusions Including Changes in the Panel's Recommendations and in the Agency's Previous Recommendations

FDA has considered the comments and other relevant information and is amending the previous tentative final monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency in this amended tentative final monograph follows.

1. All of the section numbers for health-care antiseptics in the previous tentative final monograph have been redesignated in this amendment. As a convenience to the reader, the following chart is included to show these redesignations.

REDESIGNATED SECTION NUMBERS OF THE TENTATIVE FINAL MONOGRAPH FOR ANTIMICROBIAL DRUG PRODUCTS

Old section No.	Section name	New section No.
General Provisions:		
333.1	Scope	333.401
333.3	Definitions Active Ingredients	333.403
333.20	Antimicrobial Soap	Deleted
333.30	Patient Preoperative Skin Preparation	333.410
333.50	Surgical Hand Scrub Labeling	333.410
333.80	Antimicrobial Soap	Deleted
333.85	Health-Care Personnel Handwash	333.455
333.87	Patient Preoperative Skin Preparation	333.460
333.97	Surgical Hand Scrub	333.465
333.99	Professional Labeling	Deleted

In addition, a number of format changes have been made that are consistent with the format used in recently published tentative final and final monographs.

2. The agency is proposing the term "antiseptic" as the general statement of identity for the product categories of patient preoperative skin preparation, surgical hand scrub, and health-care personnel handwash drug products. The agency is also providing manufacturers the option to provide alternative statements of identity describing only the specific intended use of the product, e.g., surgical hand scrub. When the term "antiseptic" is used as the only statement of identity on a single-use or a multiple-use product, the intended use(s) is to be included as part of the indications. For multiple use products the agency proposes that a statement of the intended use(s) should also precede the specific directions for each use. (See section I.B., comment 3.)

3. The agency is proposing that the statement of identity "antiseptic handwash" may also be used for a health-care personnel handwash. The agency is proposing to expand the indications proposed for health-care personnel handwash drug products in the previous tentative final monograph to read, "Handwash to help reduce bacteria that potentially can cause disease" or "For handwashing to decrease bacteria on the skin" (which may be followed by one or more of the following: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment.") The agency is also proposing "recommended for repeated use" as another allowable indication for this product class. (See section I.B., comment 5.)

4. The agency has replaced the previously proposed definition of an antimicrobial (active) ingredient with a definition of an "antiseptic" drug that is consistent with the definition of an antiseptic in section 201(o) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(o)). The agency is also including a definition for a health-care

antiseptic as follows: "An antiseptic containing drug product applied topically to the skin to help prevent infection or to help prevent cross contamination." The agency has also proposed revised definitions for patient preoperative skin preparations and surgical hand scrubs that reflect the agency's proposed effectiveness criteria for these products. (See section I.N., comment 28.) In addition, the agency has made minor revisions in the definitions of a health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub to reflect the revised terminology being used in this amended tentative final monograph.

5. The agency is adding to this amended tentative final monograph a definition of broad spectrum activity as follows: A properly formulated drug product, containing an ingredient included in the monograph, that possesses in vitro activity against the micro-organisms listed in § 333.470(a)(1)(ii), as demonstrated by in vitro minimum inhibitory concentration determinations conducted according to methodology established in § 333.470(a)(1)(ii). The agency is proposing to include "broad spectrum" in the definitions of the three product classes included in this tentative final monograph. (See section I.C, comment 6.)

6. The agency has reviewed the *Other Allowable Statements* proposed in the previous tentative final monograph in § 333.85 for health-care personnel handwash, in § 333.87 for patient preoperative skin preparation, and in § 333.97 for surgical hand scrub and determined that statements such as "contains antibacterial ingredient(s)," "contains antimicrobial ingredient(s)," and "non-irritating," are not related in a significant way to the safe and effective use of these products and are not necessary on products intended primarily for health-care professionals. Therefore, the agency is not including these statements in this amended tentative final monograph. The statement "recommended for repeated use," proposed for a health-care personnel handwash, has been included as an "other allowable indication" in proposed § 333.455. The terms "broad spectrum" and "fast acting" are included in the definitions of all three product classes and the agency does not see the need to include this information in the required labeling. (See section I.D., comment 7.)

7. The agency is proposing revised indications for patient preoperative skin preparations in order to more precisely describe the intended uses of these products. The previous indications "kills micro-organisms," "antibacterial," and "antimicrobial" are not being included. Likewise, the indications "kills micro-organisms," "bacteriostatic," and "bactericidal" previously proposed for surgical hand scrubs are not being included in this amended tentative final monograph. The agency believes that these terms are product attributes and not indications for use and should not be included as indications in the labeling of these products.

8. Based on the recommendations of the Miscellaneous External Panel in the advance notice of proposed rulemaking for OTC alcohol drug products (47 FR 22324 at 22332), the agency is proposing "for preparation of the skin prior to an injection" as an indication for OTC alcohol and isopropyl alcohol drug products.

9. The agency is proposing in § 333.450(c) of this amended tentative final monograph the following general warning statements for all health-care antiseptic drug products:

(1) "For external use only."

(2) "Do not use in the eyes."

(3) "Discontinue use if irritation and redness develops. If condition persists for more than 72 hours consult a doctor." The agency is further proposing that the second sentence of the proposed warning in (3) above may be deleted for products labeled "For Hospital and Professional Use Only." (See section I.D., comment 8.) In addition to the general warnings proposed for OTC health-care antiseptic drug products, the agency is proposing the following warning for patient preoperative skin preparations containing isopropyl alcohol identified in § 333.412(d): "Do not use this product with electrocautery procedures." The proposed warning is based on reports of burns associated with the use of isopropyl alcohol containing patient preoperative skin preparations with electrocautery procedures. (See section II.A., paragraph 1—Summary of Ingredient Categories.)

10. Based on its review of the published literature (Refs. 1, 2, and 3), the agency has determined that the way in which health-care antiseptic drug products are used, *e.g.*, method of application, duration of scrub or wash, or use in conjunction with a device (such as a scrub brush), contributes to the effectiveness of these drug products. Therefore, instead of proposing directions for use of these products that include fixed scrub or wash durations or methods of application, the agency is proposing in §§ 333.455(c), 333.460(d), and 333.465(c) directions for use that reflect the conditions used when the antiseptic product was tested according to § 333.470(b). In addition, based on data indicating that the largest bioburden of the hands lies in the subungual region (Ref. 4), the agency is proposing that the directions for use of surgical hand scrub drug products include the following instructions for the trimming and cleansing of the nails: "Clean under nails with a nail pick. Nails should be maintained with a 1 millimeter free edge."

References

(1) Ayliffe, G.A.J., "Surgical Scrub and Skin Disinfection," Infection Control, 5:23–27, 1984.

(2) Maki, D.G., "The Use of Antiseptics for Handwashing by Medical Personnel," *Journal of Chemotherapy*, 1:3–11, 1989.

(3) Ojajarvi, J., "Effectiveness of Hand Washing and Disinfection Methods in Removing Transient Bacteria After Patient Nursing," *Cambridge University Journal of Hygiene*, 85:193–203, 1980.

(4) Leyden, J. *et al.*, "Subungual Bacteria of the Hand: Contribution to the Glove Juice Test; Efficacy of Antimicrobial Detergents," *Infection Control Hospital Epidemiology*, 10:451–454, 1989.

11. The agency is aware that some manufacturers provide technical information relating to the antimicrobial activity of their health-care antiseptic drug products in the form of technical information bulletins. The agency considers such bulletins to be labeling under the provisions of the act. Section 201(m) of the act (21 U.S.C. 321(m)) defines the term "labeling" as "all labels and other written, printed, or graphic matter (1) upon any article or any of the containers or wrappers, or (2) accompanying such article." As labeling, technical information bulletins are subject to the OTC drug review.

The agency has no objection to the inclusion of technical information relating to the antimicrobial activity of these OTC drug products in the labeling of products intended for health-care professionals only. Therefore, in this amended tentative final monograph the agency is proposing that manufacturers have the option of including data derived from the in vitro and clinical effectiveness tests included in § 333.470 of the proposed monograph as additional labeling for products labeled and marketed "For Hospital and Professional Use Only." In order that such additional information provide a standardized comparison of the effectiveness of these OTC drug products, the agency is further proposing that only data on the antimicrobial activity of these OTC drug products derived from the effectiveness tests included in § 333.470 of this

proposed monograph be included in the labeling of these OTC drug products. At the present time, claims of product effectiveness against organisms other than those included in § 333.470(a)(1)(ii) will require an NDA containing information supporting the deviation from the monograph in accord with § 330.11.

12. Based on the wound healing data from studies of test wounds in laboratory animals that were discussed in the first aid antiseptic segment of this amended tentative final monograph (comment 37, 56 FR 33644 at 33662), the agency has reevaluated the labeling for iodine tincture as a patient preoperative skin preparation and is not including the warning "Do not apply this product with a tight bandage, as a burn may result."

13. The agency has determined that data and reports have not provided specific evidence that repeated use of health-care antiseptics has brought about overgrowth of gram-negative bacteria, particularly *Pseudomonas*. Therefore, the previously proposed caution in § 333.99(a) concerning this overgrowth is not being included in this amended tentative final monograph. (See section I.D, comment 9.) The warnings proposed in § 333.99 (b) and (c) of the previous tentative final monograph are not being included in this amendment because these warnings apply to quaternary ammonium compounds which currently are not Category I for health-care antiseptic uses. (See section I.J., comment 20.)

14. The agency is not including the warning proposed by the Miscellaneous External Panel in § 333.98(c)(2) for products containing isopropyl alcohol, "Use only in a well-ventilated area; fumes may be toxic." As discussed in section II.B., paragraph 32 of the segment of this rulemaking covering first aid antiseptics (56 FR 33644 at 33556), the agency invites comment on the need for such a warning, including any reports of adverse reactions due to inhalation that have not yet been brought to the agency's attention.

15. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using the word "physician" or the word "doctor." This amended tentative final monograph proposes that option in § 333.450(e).

16. Based on the withdrawal of the majority of the comments on chlorhexidine gluconate as a health-care antiseptic, sufficient data upon which to make a safety and effectiveness determination are no longer present in the rulemaking. (See section I.F., comment 11.)

17. The agency has reviewed the data submitted on chloroxylenol and is classifying chloroxylenol 0.24 percent to 3.75 percent as Category I for safety and Category III for effectiveness for short-term use (patient preoperative skin preparation) and Category III for both safety and effectiveness for long-term uses (antiseptic handwash or health-care personnel handwash and surgical hand scrub). (See section I.G., comment 12.)

18. In § 333.30(a) of the previous tentative final monograph, the agency included United States Pharmacopeia (U.S.P.) specifications for iodine tincture and topical solution. In this amended tentative final monograph, the agency is identifying these Category I patient preoperative products as iodine tincture U.S.P. and iodine topical solution U.S.P.

19. The agency has reviewed the submitted data on hexachlorophene and concludes that the data do not address the safety concerns expressed by the Antimicrobial I Panel on this ingredient. Therefore, the agency is proposing that hexachlorophene remain available by prescription only. (See section I.H., comment 13.)

20. The agency has evaluated a "mixed iodophor" consisting of iodine complexed by ammonium ether sulfate and polyoxyethylene sorbitan monolaurate and found it to be safe for use as a surgical hand scrub and health-care personnel handwash, but there are insufficient data available to determine its effectiveness for these uses. Therefore, it is being classified in Category III. (See section I.I., comment 15.) The other iodine-surfactant complexes classified by the Antimicrobial I Panel remain in Category III for health-care uses due to a lack of data.

21. The agency is including povidone-iodine 5 to 10 percent as a Category I health-care antiseptic ingredient for use as a surgical hand scrub, patient preoperative skin preparation, and antiseptic handwash or health-care personnel handwash. (See section I.I., comment 17.) As discussed in section I.I., comment 16, the agency is not including the warning about the interaction of iodophors and starch-containing compounds proposed in comment 66 of the previous tentative final monograph (43 FR 1221). The agency is also not including professional labeling to limit the molecular weight of povidone-iodine or special warnings related to the molecular weight of povidone-iodine. (See section I.I., comment 18.)

22. The agency has evaluated the data submitted on benzalkonium chloride and determined that the data are not sufficient to establish the efficacy of this ingredient as a patient preoperative skin preparation. (See section I.J., comment 20.) No data were received on other health-care uses of this ingredient or health-care uses of the two other quaternary ammonium compounds (benzethonium chloride and methylbenzethonium chloride) classified by the Antimicrobial I Panel. Accordingly, quaternary ammonium compounds remain in Category III as health-care antiseptics.

23. The agency has reviewed data submitted on sodium oxychlorosene, an ingredient not previously classified for OTC topical antiseptic use, and is placing this ingredient in Category III for both safety and effectiveness. (See section I.K., comment 22.)

24. The agency has reclassified triclosan up to 1 percent from Category II to Category III as a health-care antiseptic for use as a patient preoperative skin preparation, antiseptic handwash or health-care personnel handwash, and surgical hand scrub. While submitted data indicate that triclosan—when properly formulated—may be effective, data that meet the criteria described in section I.N., comment 28 are needed to establish effectiveness. In addition, based upon submitted safety data and other information, the agency has reclassified the ingredient from Category III to Category I for safety for short-term use as a patient preoperative skin preparation. Triclosan remains classified in Category III for long-term use (antiseptic handwash or health-care personnel handwash and surgical hand scrub). (See section I.L., comment 23.)

25. The agency is proposing a number of Category I health-care antiseptic ingredients in this document. All of the ingredients included in this proposal as Category I health-care antiseptic ingredients are standardized and characterized for quality and purity and are included as articles in the current United States Pharmacopeia or National Formulary (U.S.P./N.F.) (Ref. 1). However, a number of other ingredients being considered in this rulemaking, *e.g.*, triclosan and triclocarban are not listed in the U.S.P./N.F. For an active ingredient to be included in an OTC

drug final monograph, in addition to information demonstrating safety and effectiveness, it is necessary to have publicly available sufficient chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products.

The agency believes that it would be appropriate for parties interested in upgrading nonmonograph ingredients to monograph status to develop with the United States Pharmacopeial Convention appropriate standards for the quality and purity of health-care antiseptic ingredients that are not already included in official compendia. However, should interested parties fail to provide necessary information so that appropriate standards may be established, ingredients otherwise eligible for monograph status will not be included in the final monograph.

Reference

(1) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, 1989, pp. 34, 703, 731, and 1119.

26. The agency is proposing testing requirements for patient preoperative skin preparation, antiseptic handwash or health-care personnel handwash, and surgical hand scrub drug products in § 333.470 of this tentative final monograph. As part of the effectiveness criteria for a patient preoperative skin preparation, the agency is proposing new testing requirements for products labeled with the proposed indication "for the preparation of the skin prior to an injection." (See section I.N., comment 28.)

27. The agency acknowledges that deodorancy is considered a cosmetic claim. However, some deodorant soap products also bear antimicrobial claims. The agency stated in comment 10 of the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33648) that deodorant soap products making antimicrobial claims are considered to be drugs and that the testing guidelines for antimicrobial claims would be addressed in this rulemaking. Any deodorant soap product containing a monograph ingredient may be labeled with antimicrobial claims provided the product meets the testing requirements for health-care antiseptic drug products or surgical hand scrubs as described under proposed § 333.470.

The agency stated in the previous tentative final monograph for topical antimicrobial drug products (43 FR 1210 at 1244) that actual claims of deodorancy should correlate the microbial reduction achieved in a modified Cade handwashing test to an "adequately designed and executed deodorancy test, such as controlled sniff test." Several comments to that proposal objected to such a correlation of deodorancy and microbial reduction. However, none of the comments provided satisfactory data to enable the agency to include any test in a monograph as a standard for deodorancy due to antimicrobial activity. Specific testing for antimicrobial claims for deodorancy has not yet been developed. The agency intends to review any comments or methods submitted for such a purpose in response to this publication and invites comments and data on this topic.

28. The Panel's evaluation of OTC topical antimicrobial drug products did not include an evaluation of the use of these products by the food industry as hand sanitizers or dips. Historically, hand sanitizers and dips have been marketed as hand cleansers for use by food handlers in federally inspected meat and poultry processing plants and in food handling establishments. Regulation of these products has been under the jurisdiction of the U. S. Department of Agriculture. However, it has come to the agency's attention that many of these products include label claims that the agency considers drug claims, *i.e.*, "antibacterial handwash," "kills germs and bacteria on contact," or "effectively reduces bacterial flora of the skin". (See comment 10 of the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33648).) Examination of the labeling of these products (Ref. 1) has led the agency to conclude that the intended use of these products, *i.e.*, the reduction of micro-organisms on human skin for the purpose of the prevention of disease caused by contaminated food, makes them drugs under the provisions of the act. Section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) defines a "drug" as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man * * *."

The safety and effectiveness of active ingredients in these products for drug use needs to be demonstrated. Therefore, the agency is including evaluation of the safety and effectiveness of topical antimicrobial active ingredients indicated for use as hand sanitizers or dips in the rulemaking for OTC topical antimicrobial drug products. Accordingly, the agency invites the submission of data, published or unpublished, and any other information pertinent to the use of topical antimicrobial ingredients in hand sanitizers or dips. The agency also invites comment on applicable effectiveness standards for these products. These data and information will facilitate the agency's review and aid in its determination as to whether these OTC drug products for human use are safe, effective, and not misbranded under their recommended conditions of use. This evaluation will provide all interested parties an opportunity to present for consideration the best data and information available to support the stated claims for these products. The agency suggests that all submissions be in the format described in 21 CFR 330.10(a)(2).

In order to be eligible for review under the OTC drug review procedures, the ingredient must have been marketed in a hand sanitizer or dip to a material extent and for a material time (21 U.S.C. 321(p)(2)). The submission of data should include information that demonstrates that the ingredient(s) has been marketed as a hand sanitizer or dip to a material extent and for a material time. Products with ingredients under consideration in the OTC drug review may be marketed (at the same dosage strength and in the same dosage form) under the manufacturer's good faith belief that the product is generally recognized as safe and effective and not misbranded and in accord with FDA's enforcement policies related to the OTC drug review. (See FDA's Compliance Policy Guides 7132b.15 and 7132b.16.) Such products are marketed at the risk that the agency may adopt a position requiring relabeling, recall, or other regulatory action.

The agency notes that antimicrobial hand sanitizers/dips marketed for use in food handling/processing are typically labeled for a variety of other antimicrobial uses that may include various animal "drug" uses and the disinfection of inanimate objects. These other uses of hand sanitizer or dips will not be included in the agency's evaluation as part of this rulemaking.

Reference

(1) Labeling for hand sanitizer products, in OTC Vol. 230001, Docket No. 75N–183H, Dockets Management Branch.

29. The agency is proposing to remove a portion of § 369.21 applicable to OTC health-care antiseptic drug products when the final monograph eventually becomes effective because a portion of the regulations will be superseded by the final monograph. The item proposed for removal is the entry for "ALCOHOL RUBBING COMPOUND" in § 369.21.

III. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order

12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This proposed rule increases the number of ingredients tentatively classified as generally recognized as safe and effective for use in OTC health-care antiseptic drug products from the previous proposal and, if finalized as proposed, would reduce the need for further safety and effectiveness testing for a number of health-care antiseptic drug products. The detailed testing procedures included in the proposed rule should assist manufacturers of products containing ingredients not included in the proposed monograph, due to a lack of demonstrated effectiveness, in performing the tests that would demonstrate effectiveness so the ingredients can be included in the final rule. The testing procedures will also provide manufacturers guidance on testing requirements for regulatory compliance. Products that contain ingredients for which safety and effectiveness are not established will require reformulation. The proposed monograph includes ingredients that may be used if reformulation becomes necessary. All products will need some relabeling. One year will be provided from the date of publication of the final rule for any necessary relabeling or reformulation. Accordingly, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC health-care antiseptic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulation. Comments regarding the impact of this rulemaking on OTC health-care antiseptic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on health-care antiseptic drug products, a period of 180 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before December 14, 1994, submit to the Dockets Management Branch, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 14, 1994. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before June 19, 1995, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before August 17, 1995. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch. Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 17, 1995. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Therefore, the agency is proposing to amend 21 CFR part 333 by adding new subpart E, consisting of §§ 333.401 through 333.470, and to amend 21 CFR part 369 by amending § 369.21 in order to establish conditions under which OTC health-care antiseptic drug products are generally recognized as safe and effective and not misbranded.

List of Subjects

21 CFR Part 333

Labeling, Over-the-counter drugs, Incorporation by reference.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 333 and 369 be amended as follows:

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 333 is revised to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. New subpart E, consisting of §§ 333.401 through 333.470, is added to read as follows:

Subpart E—Health-Care Antiseptic Drug Products

Sec.

Subpart E—Health-Care Antiseptic Drug Products

§ 333.401 Scope.

(a) An over-the-counter health-care antiseptic drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each of the general conditions established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

§ 333.403 Definitions.

As used in this subpart:

(a) *Antiseptic drug.* In accordance with section 201(o) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(o)), "The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body."

(b) *Broad spectrum activity.* A properly formulated drug product, containing an ingredient included in the monograph, that possesses in vitro activity against the micro-organisms listed in § 333.470(a)(1)(ii), as demonstrated by in vitro minimum inhibitory concentration determinations conducted according to methodology established in § 333.470(a)(1)(ii).

(c) *Health-care antiseptic.* An antiseptic containing drug product applied topically to the skin to help prevent infection or to help prevent cross contamination.

(1) *Antiseptic handwash or health-care personnel handwash drug product.* An antiseptic containing preparation designed for frequent use; it reduces the number of transient micro-organisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying; it is broad spectrum, fast acting and, if possible, persistent.

(2) *Patient preoperative skin preparation drug product.* A fast acting, broad spectrum, and persistent antiseptic containing preparation that significantly reduces the number of micro-organisms on intact skin.

(3) *Surgical hand scrub drug product.* An antiseptic containing preparation that significantly reduces the number of micro-organisms on intact skin; it is broad spectrum, fast acting, and persistent.

§ 333.410 Antiseptic handwash or health-care personnel handwash active ingredients.

The active ingredient of the product consists of any of the following within the specified concentration established for each ingredient properly formulated to meet the test requirements in § 333.470, and the product is labeled according to §§ 333.450 and 333.455:

(a) Alcohol 60 to 95 percent by volume in an aqueous solution denatured according to Bureau of Alcohol, Tobacco and Firearms regulations in 27 CFR part 20; or

(b) Povidone-iodine 5 to 10 percent.

§ 333.412 Patient preoperative skin preparation active ingredients.

The active ingredient of the product consists of any of the following within the specified concentration established for each ingredient properly formulated to meet the test requirements in § 333.470, and the product is labeled according to §§ 333.450 and 333.460:

(a) Alcohol 60 to 95 percent by volume in an aqueous solution denatured according to Bureau of Alcohol, Tobacco and Firearms regulations in 27 CFR part 20;

(b) Iodine tincture U.S.P.;

(c) Iodine topical solution U.S.P.;

(d) Isopropyl alcohol 70 to 91.3 percent by volume in an aqueous solution; and

(e) Povidone-iodine 5 to 10 percent.

§ 333.414 Surgical hand scrub active ingredients.

The active ingredient of the product consists of any of the following within the specified concentration established for each ingredient properly formulated to meet the test requirements in § 333.470, and the product is labeled according to §§ 333.450 and 333.465:

(a) Alcohol 60 to 95 percent by volume in an aqueous solution denatured according to Bureau of Alcohol, Tobacco and Firearms regulations in 27 CFR part 20; or

(b) Povidone-iodine 5 to 10 percent.

§ 333.420 Permitted combinations of active ingredients.

[Reserved]

§ 333.450 Labeling of health-care antiseptic drug products.

(a) *Statement of identity.* The labeling of a single-use product contains the established name of the drug, if any, and identifies the product as an "antiseptic" and/or with the appropriate statement of identity described in §§ 333.455(a), 333.460(a), or 333.465(a). The labeling of a multiple-use product contains the established name of the drug, if any, and may use the single statement of identity "antiseptic" and/or the appropriate statements of identity described in §§ 333.455(a), 333.460(a), and 333.465(a). When "antiseptic" is used as the only statement of identity on a single-use or a multiple-use product, the intended use(s), such as patient preoperative skin preparation, is to be included under the indications. For multiple-use products, a statement of the intended use should also precede the specific directions for each use.

(b) *Indications.* The labeling of a single use antiseptic drug product contains the labeling identified in §§ 333.455, 333.460, or 333.465, as appropriate. Multiple-use products contain the labeling from any two or all three of §§ 333.455, 333.460, and 333.465. Indications, warnings, and directions applicable to each intended use of the product may be combined to eliminate duplicative words or phrases so that the resulting indications, warnings, and directions are clear and understandable.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "For external use only."

(2) "Do not use in the eyes."

(3) "Discontinue use if irritation and redness develop. If condition persists for more than 72 hours consult a doctor."

(4) *For products containing any ingredient identified in §§ 333.410(a), 333.412(a) and (d), and 333.414(a).* The following statement shall immediately follow the heading "Warnings": "Flammable, keep away from fire or flame." [sentence in boldface type]

(d) The second sentence of the warning in paragraph (c)(3) of this section may be omitted from the labeling of products labeled "For Hospital and Professional Use Only."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in §§ 333.455, 333.460, and 333.465.

(f) *Optional labeling information.* Technical information relating to the antimicrobial activity of products that is limited to data derived from the in vitro and clinical effectiveness tests included in § 333.470 may be included as

additional labeling for products labeled for "Hospital and Professional Use Only."

§ 333.455 Labeling of antiseptic handwash or health-care personnel handwash drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antiseptic," as stated above under § 333.450(a), and/or "antiseptic handwash," or "health-care personnel handwash."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph that are applicable to the product. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products labeled as a health-care personnel handwash.* "Handwash to help reduce bacteria that potentially can cause disease" or "For handwashing to decrease bacteria on the skin" (which may be followed by one or more of the following: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment.")

(2) *For products labeled as an antiseptic handwash.* "For handwashing to decrease bacteria on the skin" (which may be followed by one or more of the following: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment.")

(3) *Other allowable indications for products labeled as either antiseptic or health-care handwash.* The labeling of the product may also contain the following phrase: "Recommended for repeated use."

(c) *Directions.* The labeling of the product contains the following statements, under the heading "Directions," that reflect the conditions used when the product was tested according to § 333.470(b)(2):

(1) *For products to be used with water.* "Wet hands and forearms. Apply 5 milliliters (teaspoonful) or palmful to hands and forearms. Scrub thoroughly for" (insert wash duration used when tested according to § 333.470(b)(2)). (Insert any applicable statements about also using a device, such as a scrub brush.) "Rinse and repeat."

(2) *For products to be used without water.* "Place a 'palmful' (5 grams) of product in one hand. Spread on both hands and rub into the skin until dry (approximately 1 to 2 minutes). Place a smaller amount (2.5 grams) into one hand, spread over both hands to wrist, and rub into the skin until dry (approximately 30 seconds)" or "Wet hands thoroughly with product and allow to dry without wiping."

§ 333.460 Labeling of patient preoperative skin preparation drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antiseptic," as stated under § 333.450(a), and/or "patient preoperative skin preparation."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing ingredients identified in § 333.412 (a), (b), (c), and (e).* (i) "For preparation of the skin prior to surgery."

(ii) "Helps reduce bacteria that potentially can cause skin infection."

(2) *For products containing alcohol identified in § 333.412(a).* In addition to the indications listed in § 333.460(1), the labeling may also include the statement "For preparation of the skin prior to an injection."

(3) *For products containing isopropyl alcohol identified in § 333.412(d).* "For preparation of the skin prior to an injection."

(c) *Warnings.* For products containing 70 percent or more isopropyl alcohol the following warning shall immediately follow the warning statement in § 333.450(c)(4): "Do not use with electrocautery procedures."

(d) *Directions.* The labeling of the product contains the following statements, under the heading "Directions," that reflect the conditions used when the product was tested according to § 333.470(b)(3):

(1) *For products containing any ingredient identified in § 333.412(a), (d), and (e) that are intended to remain on the skin after application.* "Clean the area. Apply product to the operative site prior to surgery" (insert method of application, including any device used, when tested according to § 333.470 (b)(3).) If appropriate, insert "Dry and repeat procedure."

(2) *For products containing any ingredient identified in § 333.412(b) or (c) that are intended to be removed from the skin after application.* "Apply product to the operative site prior to surgery" (insert method of application, including any device used, when tested according to § 333.470(b)(3).) "When product dries, remove immediately with 70 percent alcohol, or use as directed by a physician."

§ 333.465 Labeling of surgical hand scrub drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antiseptic," as stated above under § 333.450(a), and/or "surgical hand scrub."

(b) *Indication.* The labeling of the product states, under the heading "Indication," the following: "Significantly reduces the number of micro-organisms on the hands and forearms prior to surgery or patient care." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Directions.* The labeling of the product contains the following statements, under the heading "Directions," that reflect the conditions used when the product was tested according to § 333.470(b)(1):

(1) *For products to be used with water.* "Clean under nails with a nail pick. Nails should be maintained with a 1 millimeter free edge. Wet hands and forearms. Apply 5 milliliters (teaspoonful) or palmful to hands and forearms. Scrub thoroughly for (insert scrub duration used when tested according to § 333.470(b)(1)) "with a sterile" (insert applicable device), "paying particular attention to the nails, cuticles, and interdigital spaces. Rinse and repeat scrub" (if applicable, insert instructions for second scrub used when

tested according to § 333.470(b)(1), if different from the first).

(2) *For products to be used without water.* "Clean under nails with a nail pick. Nails should be maintained with a 1 millimeter free edge. Place a 'palmful' (5 grams) of product in one hand. Spread on both hands, paying particular attention to the nails, cuticles, and interdigital spaces, and rub into the skin until dry (approximately 1 to 2 minutes). Place a smaller amount (2.5 grams) into one hand, spread over both hands to wrist, and rub into the skin until dry (approximately 30 seconds)."

§ 333.470 Testing of health-care antiseptic drug products.

(a) *General testing criteria.* The procedures in this section are designed to characterize the effectiveness of antiseptic drug products formulated for use as an antiseptic handwash or health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub. Requests for any modifications of the testing procedures in this section or alternative assay methods are to be submitted in accordance with paragraph (d) of this section.

(1) *In vitro testing.* The following tests must be performed using the antiseptic ingredient, the vehicle, and the finished product for all drug product classes:

(i) Determine the in vitro antimicrobial spectrum of the active ingredient, the vehicle, and the final formulation using both standard cultures and recently isolated strains of each species. A series of recently isolated mesophilic strains, including members of the normal flora and cutaneous pathogens (50 isolates of each species, half of which must be fresh clinical isolates), are to be selected.

(ii) Determine the minimal inhibitory concentrations (MIC) using methodology established by the National Committee for Clinical Laboratory Standards and entitled "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically," Document M7–A2, 2d ed., 10:8, 1990, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the National Committee for Clinical Laboratory Standards, 771 East Lancaster Ave., Villanova, PA 19085, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC. Twenty-five fresh clinical isolates and 25 laboratory strains of the organisms listed in this section are to be included. All in vitro tests must include the American Type Culture Collection (ATCC) reference strains (available from American Type Culture Collection, 12301 Parklawn Dr., Rockville, MD 20852) specified in paragraphs (a)(1)(ii)(A) and (a)(1)(ii)(B) of this section. The agency requires that these organisms be used in testing unless data can be presented to the agency that other organisms are equally representative of organisms associated with nosocomial infection. There must be no claims, either direct or by implication, that a product has any activity against an organism or that it reduces the number of organisms for which it has not been tested. The following organisms are to be included (note: special media and environmental conditions may be required):

(A) *Gram negative organisms: Acinetobacter* species; *Bacteroides fragilis*; *Haemophilus influenza*; *Enterobacter* species; *Escherichia coli* (ATCC Nos. 11229 and 25922); *Klebsiella* species, including *Klebsiella pneumonia*; *Pseudomonas aeruginosa* (ATCC Nos. 15442 and 27853); *Proteus mirabilis*; and *Serratia marcescens* (ATCC No. 14756).

(B) *Gram positive organisms*: Staphylococci: *Staphylococcus aureus* (ATCC Nos. 6538 and 29213); Coagulase-negative Staphylococci: *Staphylococcus epidermidis* (ATCC No. 12228), *Staphylococcus hominis*, *Staphylococcus haemolyticus*, and *Staphylococcus saprophyticus*; *Micrococcus luteus* (ATCC No. 7468); and Streptococci: *Streptococcus pyogenes*, *Enterococcus faecalis* (ATCC No. 29212), *Enterococcus faecium*, and *Streptococcus pneumoniae*.

(C) *Yeast*: *Candida* species and *Candida albicans*.

(iii) Determine the possible development of resistance to the chemical. Two approaches to determining the emergence of resistance to a particular antimicrobial are to be used. The first approach involves a determination of the evolution of a point mutation by the sequential passage of an organism through increasing concentrations of the antimicrobial included in the culture medium. The second approach is a thorough survey of the published literature to determine whether resistance has been reported for the antimicrobial ingredient. The survey is to include information on the microbial contamination of marketed products containing the antimicrobial ingredient in question irrespective of drug concentration. The survey is to cover all countries in which products containing the active ingredient are marketed. Any information submitted in a foreign language should include a translation. Alternate approaches to determining the development of resistance can be submitted as a petition in accord with § 10.30 of this chapter. The petition is to contain sufficient data to show that the alternate approach provides a reliable indication of the development of resistance to a particular antimicrobial ingredient.

(iv) *Time-kill studies.* (A) The assessment of the in vitro spectrum of the antimicrobial provides information on the types of genera and species that may be considered susceptible under the conditions of the test procedure described in paragraph (a)(1)(ii) of this section. However, information is also required that allows an assessment of how rapidly the antimicrobial product produces its effect. Such information may be derived from in vitro time-kill curve studies using a selected battery of organisms and a specified drug concentration.

(B) The satisfactory performance of the test product as assessed by the results of the MIC studies, the time-kill studies, and the simulated in vivo clinical trials of organisms representing the resident microbial flora can then be used to assess the effectiveness of the test product for the transient microbial flora most commonly encountered in the clinical setting. This procedure is required because methods, other than the health-care personnel hand test, do not exist for assessing the in vivo effectiveness of test products versus the transient microbial flora.

(C) It is recognized that a generally accepted or standardized method that may be used in conducting in vitro time-kill studies is not available, but the agency encourages the submission of proposed methods that may be considered applicable to this test. Many variables that should be considered in the development of a method have been addressed for antibiotics and are also applicable to these products. Such variables are described by Schoenknecht, F. D., L. D. Sabath, and C. Thornsberry, "Susceptibility Tests: Special Tests," in the "Manual of Clinical Microbiology," 4th ed., edited by E. H. Lennette et al., American Society for Microbiology, Washington, pp. 1,000–1,008, which is incorporated by reference in accordance with 5 U.S.C 552(a) and 1 CFR part 51. Copies are available from the American Society for Microbiology, Washington, DC, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the Federal Register, 800 Nort

Capitol St. NW., suite 700, Washington, DC.

(D) The procedure to be used is to incorporate the recommendations described on page 1,004 of the chapter in the "Manual of Clinical Microbiology" cited in paragraph (a)(1)(iv)(C) of this section with the following modifications. Because the time frames of greatest interest for antiseptic drug products intended for health-care personnel handwash, surgical hand scrub, and patient preoperative skin preparation use are 1 to 30 minutes, the time-kill studies are to focus on these time frames and are to include enumerations at times 0, 3, 6, 9, 12, 15, 20, and 30 minutes. Enumerate the bacteria in the sampling solution by a standard plate count procedure such as that described in "Standard Methods for the Evaluation of Dairy Products" (available from American Public Health Association, Inc., 1015 15th St. NW., Washington, DC 20005), but using soybean-casein digest agar and a suitable inactivator for the antimicrobial where necessary. The suitability of the inactivator is to be demonstrated using a procedure such as described in E 1054, "Test Methods for Evaluating Inactivators of Antimicrobial Agents Used in Disinfectant, Sanitizer, and Antiseptic Products," in "Annual Book of ASTM Standards," vol. 11.04, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from The American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and Research (HFD–810), 5600 Fishers Lane, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC. The battery of organisms selected is to represent the resident microbial flora most commonly encountered under actual use conditions of the test product and the transient microbial flora most likely to be encountered by health-care professionals in clinical settings. Therefore, the micro-organisms to be used in these time-kill studies are to be the standard ATCC strains identified in paragraph (a)(1)(ii) of this section. The drug concentration to be tested should be a tenfold dilution of the finished product.

(2) *In vivo testing.* The following tests, approximating use conditions for the clinical evaluation of each label claim of the finished product, are to be carried out using the finished product for the product classes specified.

(i) Test method for the evaluation of surgical hand scrub drug products. The procedure to be used (paragraph (b)(1)(iii) of this section) is a modification of the standard testing procedure for the evaluation of surgical hand scrub drug products published by the American Society for Testing and Materials, "Standard Method for Evaluation of Surgical Hand Scrub Formulation, Designation E 1115," in "The Annual Book of ASTM Standards," vol. 11.04, American Society for Testing and Materials, Philadelphia, pp. 201–204, 1986, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from The American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(ii) Test method for the evaluation of health-care antiseptic handwash or health-care personnel handwash drug products. The procedure to be used (paragraph (b)(2)(iii) of this section) is a modification of the standard testing procedure for the evaluation of health-care antiseptic handwash drug products published by the American Society for Testing and Materials, "Standard Method for the Evaluation of Health Care Handwash Formulation, Designation E1174," in "The Annual Book of ASTM Standards," vol. 11.04, American Society for Testing and Materials, Philadelphia, pp. 209–212, 1987, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from The American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(iii) Test method for the evaluation of patient preoperative skin preparation drug products. The procedure to be used (paragraph (b)(3)(iii) of this section) is a modification of the standard testing procedure for the evaluation of patient preoperative skin preparations published by the American Society for Testing and Materials, "Standard Test Method for the Evaluation of a Patient Preoperative Skin Preparation, Designation 1173," in "The Annual Book of ASTM Standards," vol. 11.04, American Society for Testing and Materials, Philadelphia, pp. 205–208, 1987, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from The American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(b) *Specific testing criteria*—(1) *Effectiveness testing of a surgical hand scrub.* A surgical hand scrub drug product in finished form suitable for topical application will be recognized as effective provided that the formulated drug product at its recommended use concentration:

(i) Contains an ingredient in § 333.414 (a) or (b).

(ii) Demonstrates in vitro activity against organisms as described in paragraph (a)(1)(ii) of this section.

(iii) When tested, in vivo, by the test procedure for the evaluation of surgical hand scrub drug products in paragraph (b)(1)(iii) of this section, reduces the number of bacteria 1-$\log_{10}$ on each hand within 1 minute and the bacterial cell count on each hand does not subsequently exceed baseline within 6 hours on the first day, and produces a 2-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the second day of enumeration, and a 3-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the fifth day when compared to the established baseline.

(A) *Apparatus*—(*1*) *Colony Counter.* Any of several types may be used.

(*2*) *Incubator.* Any incubator capable of maintaining a temperature of 30±2 °C may be used.

(*3*) *Sterilizer.* Any suitable steam sterilizer capable of producing conditions of sterility is acceptable.

(*4*) *Timer (stop clock).* A timer that can be read in minutes and seconds.

(*5*) *Hand washing sink.* A sink of sufficient size to permit panelists to wash without touching hands to sink surface or other panelists.

(*6*) *Water faucet(s).* Water faucets should be located above the sink at a height that permits the hands to be held higher than the elbows during the washing procedure. (It is desirable for the height of the faucets to be adjustable.)

(*7*) *Tap water temperature regulator and temperature monitor.* Device(s) to monitor and regulate water temperature to 40±2 °C.

(B) *Materials and reagents*—(*1*) *Petri dishes.* Petri dishes for performing standard plate count should be 100 by 15 millimeters.

(2) *Bacteriological pipets.* Pipets of 10.0 and 2.2 or 1.1 milliliter capacity are recommended.

(3) *Water-dilution bottles.* Any sterilizable glass container having a 150 to 200 milliliter capacity and tight closures may be used.

(4) *Baseline control soap.* A liquid castile soap or other liquid soap containing no antimicrobial.

(5) *Gloves.* Sterile loose fitting gloves of latex, unlined, not possessing antimicrobial properties.

(6) *Test formulation.* Directions used to demonstrate the effectiveness of the test formulation are to be the same as those proposed for the use of the product including the use of a nail cleaner and/or brush, if indicated. If no directions are available, use directions provided in paragraph (b)(1)(iii)(J)(3) of this section.

(7) *Positive control formulation.* Any surgical hand scrub formulation approved by the Food and Drug Administration is acceptable.

(8) *Sampling solution.* (*i*) Dissolve 0.4 gram potassium phosphate, monobasic, 10.1 gram sodium phosphate, dibasic, and 1 gram Triton X–100 in 1 liter distilled water. Adjust to pH 7.8 with 0.1 Normal hydrochloric acid or 0.1 Normal sodium hydroxide. Dispense 50 to 100 milliliter volumes into water dilution bottles, or other suitable containers, and sterilize for 20 minutes at 121 °C. Include in the sampling solution used to collect bacterial samples from the hand following the final wash with the test formulation an antimicrobial inactivator specific for the test formulation being evaluated.

(*ii*) A definitive recommendation regarding the inclusion of an inactivator prior to the final wash cannot be made. The questions of whether residual neutralizer on the skin will reduce the effectiveness of the test formulation in subsequent washes and result in higher than expected bacterial counts and whether or not samples can be processed rapidly enough to avoid a decreased bacterial count due to the continued action of the test formulation should be considered when the decision concerning the use of a neutralizer in sampling solutions used for bacterial collection prior to the final wash is made. Whatever the decision, to facilitate the comparison of results across studies, the investigator is to indicate whether or not a neutralizer has been included.

(9) *Dilution fluid.* Butterfield's phosphate buffered water adjusted to pH 7.2 and containing an antimicrobial inactivator specific for the test formulation. Adjust pH with 0.1 Normal hydrochloric acid or 0.1 Normal sodium hydroxide.

(10) *Soybean-casein digest agar.* Supplemental polysorbate 80 (0.5 to 10 grams/liter) is to be added to the agar to stimulate the growth of lipophilic organisms. A suitable antimicrobial inactivator is also to be added.

(11) *Fingernail cleaning sticks.*

(12) *Sterile hand brushes (required only if specified for use with test formulation).* Products that specify the use of a device in conjunction with the antimicrobial are to include this information in the product labeling. The device is an integral part of the study. If gauze is to be used, then the product labeling is to reflect this condition of use.

(C) *Test panelists.* Panelists shall consist of healthy adult male and female volunteers who have no evidence of dermatosis, have not received antibiotics or taken oral contraceptives 2 weeks prior to the test, and who agree to abstain from these materials as described in paragraph (b)(1)(iii)(D)(2) of this section until the conclusion of the test.

(D) *Preparation of volunteers.* (1) At least 2 weeks prior to start of the test, enroll sufficient subjects per product being tested to satisfy the statistical criteria of the clinical trial design.

(2) Instruct the volunteers to avoid contact with antimicrobials (other than the test formulation) for the duration of the test. This restriction includes antimicrobial containing antiperspirants, deodorants, shampoos, lotions, soaps, and materials such as acids, bases, and solvents. Bathing in chlorinated pools and hot tubs is to be avoided. Volunteers are to be provided with a kit of nonantimicrobial personal care products for exclusive use during the test and rubber gloves to be worn when contact with antimicrobials cannot be avoided.

(E) *Selection of evaluable subjects.* After panelists have refrained from using antimicrobials for at least 2 weeks, perform wash with baseline control soap. Subjects are not to have washed their hands 2 hours prior to the baseline count determination. After washing, determine the first estimate of the baseline population by sampling both hands and enumerating the bacteria in the sampling solution. This is day 1 of the "baseline period." Repeat this baseline determination on days 3 and 7, days 3 and 5, or days 5 and 7 of the "baseline period" to obtain three estimates of the baseline population. Any subjects exhibiting counts greater than or equal to $1.5X10^5$ after the first and second estimates of the baseline populations are obtained can be assigned to products in accordance with the randomization plan described below. Sufficient evaluable subjects must be enrolled per arm to satisfy the statistical conditions of adequacy with at least 80 percent power and a test level of 5 percent.

(F) *Number of subjects.* The number of subjects required per arm of the study can be estimated from the following equation: $n \geq 2S^2(Z_{a/2}+Z_b)^2/D^2$, where:

S^2 is your estimate of variance;

$Z_{a/2}$ corresponds to the level of the test; for a 5 percent test level = 1.96;

Z_b corresponds to the power of the test; for 80 percent power = .842; and

D is the clinical difference of significance to be ruled out; say 20 percent of the active control's mean reduction from baseline at a specific time. For example, data from a number of glove juice studies submitted over the past few years to the agency as part of applications under part 314 of this chapter were reviewed to obtain information relative to the variance of the difference from baseline for count reduction data. For 128 standard deviations extracted, it was noted that 50 percent of the values are between .90 and 1.12; 25 percent are less than .90; and 25 percent are greater than 1.12. The range is from .49 to 1.73, the 25th percentile standard deviation is 0.86, the median standard deviation is 1.01, and the 75th percentile standard deviation is 1.20. The larger the standard deviation, the larger the sample size required to rule out a difference of clinical importance. Assuming that the active control surgical hand scrub produces a mean log reduction of 2.5 at hour 3 and the test hand scrub is to be within 20 percent of this, *i.e.*, D=0.5, and if S^2= 1.02, then n=64 subjects per arm of the study. Because blocks of six are recommended, the sample size per arm is 66. The S_2=1.44 corresponds to the 75th percentile in the data set. This gives a sample size of 90 subjects per arm. The total number of evaluable subjects required for a successful trial will depend upon the estimate of variance available and the number of products that need testing.

(G) *Study design.* A randomized, blinded, parallel arm design is to be used to test the products. Due to the nature of their constituents, some test surgical hand scrubs will require not only the use of an active control arm but also use of a vehicle control arm and perhaps a placebo control arm to demonstrate efficacy. The schematic layout of sampling times is given in Table 1 as follows:

TABLE 1.—SAMPLING TIMES FOR SURGICAL HAND SCRUB EFFECTIVENESS TEST

Days	Hours			
	Baseline period	1/60	3	6
Day 0	X			
Day 1		X	X	X
Day 3 or 5		X	X	X
Day 5 or 7		X	X	X

The schematic layout of randomization of subjects in blocks of 6 is given in Table 2; in Table 2, R refers to right hand and L refers to left hand as follows:

TABLE 2.—RANDOMIZATION OF SUBJECTS FOR SURGICAL HAND SCRUB EFFECTIVENESS TEST

Subjects	Hours		
	1/60	3	6
A	R	L	
B	L		R
C		L	R
D	L	R	
E	R		L
F		R	L
Total Observations.	4	4	4

Assume N evaluable subjects are enrolled (the issue of determining N, the sample size, is discussed in paragraph (b)(1)(iii)(F) of this section). First, randomly divide the N subjects into as many treatment groups as there are products to be tested (n_t). Secondly, randomize the n_t subjects within each treatment group in blocks of six subjects in accordance with the subject allocation scheme in Table 2 of paragraph (b)(iii)(G) of this section until all n_t patients are randomized to 6 hours. Repeat this process for each of the other treatment groups.

(H) *Count determinations.* No sooner than 12 hours, nor longer than 4 days after completion of their baseline determination, subjects perform the initial scrub with the test formulations. Determine the bacterial population on the randomly designated hand of all subjects assigned to hour 1/60 in Table 2 of paragraph (b)(iii)(G) of this section immediately (within 1 minute) after scrub with the appropriate scrub formulation. Determine the bacterial counts on the designated hands at 3 and 6 hours after scrub. Determine bacterial population by sampling hands and enumerating the bacteria in the sampling solution as specified in paragraphs (b)(1)(iii)(K) and (b)(1)(iii)(L) of this section. Repeat this scrubbing and sampling procedure the next day (day 2). On day 5, repeat the sampling procedure after scrubbing with the formulations two additional times on day 2 and three times per day on day 3 and day 4, with at least a 1-hour interval between scrubs. Perform one scrub on day 5, prior to sampling. In summary, the subjects scrub a total of 11 times with each formulation, once on days 1 and 5 and 3 times per day on days 2, 3, and 4. Collect bacterial samples following the single scrubs of days 1 and 5 and following the first scrub on day 2. This procedure mimics typical usage and permits determination of both immediate and longer-term reductions.

(I) *Washing technique for baseline determinations.* (*1*) Volunteers clean under fingernails with nail stick and clip fingernails to less than or equal to 2 millimeter free edge. Remove all jewelry from hands and arms.

(*2*) Rinse hands including two thirds of forearm under running tap water 38 to 42 °C for 30 seconds. Maintain hands higher than elbows during this procedure and steps outlined in paragraphs (b)(1)(iii)(I)(*3*), (b)(1)(iii)(I)(*4*), and (b)(1)(iii)(I)(*5*) of this section.

(*3*) Wash hands and forearms with baseline control soap for 30 seconds using water as required to develop lather.

(*4*) Rinse hands and forearms for 30 seconds under tap water to thoroughly remove all lather.

(*5*) Don rubber gloves used in sampling hands and secure gloves at wrist.

(J) *Surgical scrub technique to be used prior to bacterial sampling.* (*1*) Repeat procedure outlined in paragraphs (b)(1)(iii)(I)(*1*) and (b)(1)(iii)(I)(*2*) of this section.

(*2*) Perform surgical scrub with test formulation in accordance with directions furnished with the test formulation. If no instructions are provided with the test formulation, use the 10-minute scrub procedure described in paragraph (b)(1)(iii)(J)(*3*) of this section.

(*3*) Perform 10-minute scrub procedure as follows:

(*i*) Dispense formulation into hands.

(*ii*) Set and start timer for 5 minutes (time required for the steps described in paragraphs (b)(1)(iii)(J)(*3*)(*iii*) through (b)(1)(iii)(J)(*3*)(*vii*) of this section.

(*iii*) With hands, distribute formulation over hands and lower two-thirds of forearms.

(*iv*) If scrub brush is to be used, pick up with finger tips and pass under tap to wet without rinsing formulation from hands.

(*v*) Alternatively, scrub right hand and lower two-thirds of forearm and left hand and lower two-thirds of forearm.

(*vi*) Rinse both hands, the lower two-thirds of forearms, and the brush for 30 seconds.

(*vii*) Place brush in sterile dish within easy reach.

(*viii*) Repeat the timed 5 minute scrub in paragraphs (b)(1)(iii)(J)(*3*)(*iii*) through (b)(1)(iii)(J)(*3*)(*vii*) of this section so that each hand and forearm is washed twice. The second wash and rinse should be limited to the lower one-third of the forearms and the hands.

(*ix*) Perform final rinse. Rinse each hand and forearm separately for 1 minute per hand.

(*x*) Don rubber gloves used in sampling hands and secure at wrist.

(K) *Sampling techniques.* (*1*) At specified sampling times, aseptically add 50 to 100 milliliters of sampling solution to glove and hand to be sampled, and fasten glove securely above wrist.

(*2*) After adding sampling solution, uniformly massage all surfaces of hand for 1 minute, paying particular attention to the area under the nails.

(*3*) After massaging, aseptically sample the fluid of the glove. Transfer immediately a measured volume of the sample to a serial dilution tube containing a suitable antimicrobial inactivator.

(L) *Enumeration of bacteria in sampling solution.* Enumerate the bacteria in the sampling solution by a standard plate count procedure such as that described in "Standard Methods for the Evaluation of Dairy Products" (available from American Public Health

Association, Inc., 1015 15th St. NW., Washington, DC 20005) but using soybean-casein digest agar and a suitable inactivator for the antimicrobial where necessary. The suitability of the inactivator is to be demonstrated using a procedure such as described in E 1054, "Test Methods for Evaluating Inactivators of Antimicrobial Agents Used in Disinfectant, Sanitizer, and Antiseptic Products," in "Annual Book of ASTM Standards," vol. 11.04, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from The American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC. Prepare sample dilutions in dilution fluid. Plate in duplicate. Incubate plated sample at 30 ± 2 °C for 48 hours before reading.

(M) *Determination of reduction obtained.* (*1*) At each sampling interval, determine changes from baseline counts obtained with test material.

(*2*) For a more realistic appraisal of the activity of products, all raw data should be converted to common (base 10) logarithms. Reductions should be calculated from average of the logarithms. This will also facilitate statistical analysis of data.

(N) *Comparison of test materials with a positive control material.* (*1*) In order to validate the testing procedure, equipment, and facilities, it is required that the test formulation be compared with an active control formulation. This will require an equivalent number of panelists to be assigned to the control formulation on a random basis. All test parameters will be equivalent for both formulations, except that the scrub procedure for the established formulation may be different from that of the test formulation. Both test and control formulations are to be run concurrently. Identity of the formulations used by panelists are to be blinded from those individuals counting plates and analyzing data.

(*2*) To validate the assay, compare changes from baseline counts obtained with control material at each sampling interval.

(O) *Statistical analyses.* Either of the statistical approaches to the evaluation of the data detailed in paragraph (b)(1)(iii)(O) of this section is acceptable.

(*1*) Treat data as a binomial response. That is, if a subject achieves the target reduction, it is judged a success; if not, it is a failure. A potential problem to this approach is that information may be lost. For example, if at the 1 minute time frame, a large number of subjects using one skin scrub achieve a 2-log reduction and those on the other scrub attain only a 1-log reduction, the binomial procedure will indicate both scrubs achieve the same degree of reduction. If it is believed that the binomial approach causes loss of information by not including numerical response data, then the alternate statistical analysis described in paragraph (b)(1)(iii)(O)(*2*) of this section is applicable. If the success rate is in the 90 percent range, then the variance is relatively small, sample size requirements are relatively small, and confidence intervals are reasonable. However, if the success rates drop to the 70 percent range, then relatively large sample sizes are required to obtain the same power as one gets for 90 percent success rates.

(*2*) Another option is to treat the log counts as numerical data and evaluate using the Student's t-test or similar procedure. The large variance that usually occurs with this type of data may cause problems with tests of significance and construction of confidence intervals. However, Monte Carlo techniques indicate that if entry is limited to subjects that exhibit 1.5×10^5 to 10^6 counts, then the reductions are rather homogeneous and the large variance problem is alleviated. If the variances are large, the sample size must be increased considerably to retain the same level of the test, same power, and same difference to be ruled out.

(2) *Effectiveness testing of an antiseptic handwash or health-care personnel handwash.* An antiseptic handwash or health-care personnel handwash drug product in finished form suitable for topical application will be recognized as effective provided that the formulated drug product at its recommended use concentration:

(i) Contains an ingredient in § 333.410 (a) or (b).

(ii) Demonstrates in vitro activity against organisms as described in paragraph (a)(1)(ii) of this section.

(iii) When tested, in vivo, by the test method for the evaluation of antiseptic or health-care personnel handwash drug products described in paragraph (b)(2)(iii) of this section, reduces the number of the indicator organism on each hand 2 $\log_{10}$ within 5 minutes after the first wash and demonstrates a 3-$\log_{10}$ reduction of the indicator organism on each hand within 5 minutes after the tenth wash.

(A) *Apparatus.*—(*1*) *Colony Counter.* Any of several types may be used.

(*2*) *Incubator.* Any incubator capable of maintaining a temperature of 25±2 °C may be used. This temperature is required to assure pigment production by the *Serratia marcescens.*

(*3*) *Sterilizer.* Any suitable steam sterilizer capable of producing conditions of sterility is acceptable.

(*4*) *Timer (stop clock).* A timer that can be read in minutes and seconds.

(*5*) *Hand washing sink.* A sink of sufficient size to permit panelists to wash without touching hands to sink surface or other panelists.

(*6*) *Water faucet(s).* Water faucet(s) should be located above the sink at a height that permits the hands to be held higher than the elbows during the washing procedure. (It is desirable for the height of the faucet(s) to be adjustable.)

(*7*) *Tap water temperature regulator and temperature monitor.* Device(s) to monitor and regulate water temperature to 40±2 °C.

(B) *Materials and reagents.*—(*1*) *Bacteriological pipets.* Pipets of 10.0 and 2.2 or 1.1 milliliter capacity are recommended.

(*2*) *Water-dilution bottles.* Any sterilizable glass container having a 150 to 200 milliliter capacity and tight closures may be used.

(*3*) *Erlenmeyer flask.* A 2-liter capacity for culturing test organism is recommended.

(*4*) *Baseline control soap.* A liquid castile soap or other liquid soap containing no antimicrobial.

(*5*) *Test formulation.* Directions used to demonstrate the effectiveness of the test formulation are to be the same as those proposed for the use of the product. If no directions are available, use directions provided in paragraph (b)(2)(iii)(H)(*5*) of this section.

(*6*) *Positive control formulation.* Any health-care personnel handwash formulation approved by the Food and Drug Administration is acceptable.

(*7*) *Gloves/bags.* Sterile loose fitting gloves of latex, unlined, possessing non-antimicrobial properties or sterile polyethylene bags are to be used.

(*8*) *Sampling solution.* Dissolve 0.4 gram potassium phosphate, monobasic, 10.1 gram sodium phosphate, dibasic, and 1 gram Triton X–100 in 1 liter distilled water. Adjust to ph 7.8 with 0.1 Normal hydrochloric acid or 0.1 Normal sodium hydroxide. Dispense 50 to 100 milliliter volumes into water dilution bottles, or other suitable containers, and sterilize for 20 minutes at 121 °C.

(*9*) *Dilution fluid.* Butterfield's phosphate buffered water adjusted to pH 7.2 and containing an antimicrobial inactivator specific for the test formulation. Adjust pH with 0.1 Normal

hydrochloric acid or 0.1 Normal sodium hydroxide.

(10) *Plating medium.* Soybean-casein digest agar plus a suitable inactivator.

(11) *Broth.* Soybean-casein digest: 1,000 milliliters per 2-liter flask is recommended.

(C) *Test Organism.* (1) *Serratia marcescens* ATCC No. 14756 (available from American Type Culture Collection, 12301 Parklawn Dr., Rockville, MD 20852) is to be used as a marker organism. This is a strain having stable pigmentation.

(2) The application of microorganisms to the skin may involve a health risk. Prior to applying the *Serratia marcescens* strain to the skin, the antimicrobial sensitivity profile of the strain should be determined. If the strain is not sensitive to Gentamicin, do not use it. If an infection occurs, the antibiotic sensitivity profile should be made available to the attending clinician.

(3) Following the last contamination and wash with the test formulation, the panelists' hands are to be sanitized by scrubbing with a 70 percent ethanol solution. The purpose of this alcohol scrub is to destroy any residual *Serratia marcescens.*

(4) *Preparation of marker culture suspension.* From stock culture inoculate *Serratia marcescens* ATCC No. 14756 in a 2-liter flask containing 1,000 milliliters of Soybean-casein digest broth. Incubate for 24 ± 4 hours at 25 °C. Stir or shake the suspension before each aliquot withdrawal. Assay the suspension for number of organisms by membrane filtration technique or surface inoculation at the beginning and end of the use period. Do not use a suspension for more than 8 hours.

(D) *Test panelists.* Recruit a sufficient number of healthy adult male and female human volunteers who have no clinical evidence of dermatosis, open wounds, hangnail, or other skin disorders that may affect the integrity of the test, and enroll sufficient subjects per product being tested to satisfy the statistical criteria of the clinical trial design.

(E) *Preparation of volunteers.* Instruct the volunteers to avoid contact with antimicrobials (other than the test formulation) for the duration of the test. This restriction includes antimicrobial containing antiperspirants, deodorants, shampoos, lotions, soaps, and materials such as acids, bases, and solvents. Bathing in chlorinated pools and hot tubs is to be avoided. Volunteers are to be provided with a kit of nonantimicrobial personal care products for exclusive use during the test and rubber gloves to be worn when contact with antimicrobials cannot be avoided.

(F) *Number of subjects required.* The standard deviations for antiseptic handwash or health-care personnel handwash obtained when an inoculant such as *Serratia marcescens* is used are more homogeneous than those for surgical hand scrub products discussed in paragraph (b)(1)(iii)(F) of this section. The standard deviations extracted from data submitted to the agency as part of applications under part 314 of this chapter for these drug products range from 0.31 to 0.92; the median standard deviation is 0.71. The sample size estimation equation in paragraph (b)(1)(iii)(F) of this section may be used to estimate sample sizes required. For example, assume the active control hand scrub produces an immediate mean log reduction of 2.0 and the test hand scrub is to be within 20 percent of this, i.e., D=0.4. If S^2=0.71, then n=50 subjects per arm of the study. Because blocks of 6 are recommended, the sample size per treatment arm is 54 subjects.

(G) *Study design.* Randomization of subjects to time periods and treatment to hands will be accomplished in accordance with the plan presented previously.

(H) *Procedure.* (1) *Initial wash.* After panelists have refrained from using antimicrobials for at least 7 days, perform a 30-second practice wash in the same manner as is described for the test and control formulations, except that a solution of nonantimicrobial bland soap is used. This procedure removes oil and dirt and familiarizes the panelists with the washing technique.

(2) *Contaminant suspension and hand contamination.* The contaminant is a liquid suspension of *Serratia marcescens* containing at least 10^8 organisms per milliliter. Five milliliters of the contaminant culture are dispensed onto the hands then rubbed over the surfaces of the hands, not reaching above the wrist. Application and spreading should involve about 45 seconds. The hands are then held still away from the body and allowed to air dry for 2 minutes.

(3) *Contamination schedule.* The panelists' hands are contaminated with the marker organism according to the following schedule:

(*i*) Prior to the baseline bacterial sample collection.

(*ii*) Prior to all 10 washes with the test material.

(4) *Baseline recovery.* Baseline sample is taken after contamination of the hands to determine the number of marker organisms surviving on the hands after washing with a baseline control soap as described in paragraph (b)(2)(iii)(H)(1) of this section. Bacterial sampling will follow the procedures outlined in paragraph (b)(2)(iii)(H)(6) of this section.

(5) *Wash and rinse procedure.* The wash and rinse procedure described as follows is for all washes with the test formulation. A specified volume of the test formulation is dispensed onto the hands and rubbed over all surfaces, taking caution not to lose or dilute the substance. After the material is spread, a small amount of water is added from the tap and the hands are completely lathered for a specified time period. The lower third of the forearm is also washed. After completion of the wash, hands and forearms are rinsed under tap water at 40 ±2 °C for 30 seconds. A total of 10 washes with the test formulation is involved. Bacterial samples are taken following the 1st, 3rd, 7th, and 10th washes.

(6) *Bacterial sampling.* After the 1st, 3rd, 7th, and 10th washes, place rubber gloves or polyethylene bags used for sampling on the right and left hand. Sampling should occur within 5 minutes after each of these washes. Add 50 to 100 milliliters of sampling solution to each glove and secure gloves above the wrist. After adding sampling solution, uniformly massage all surfaces of the hand for 1 minute, paying particular attention to the area under the nails. After massaging aseptically, sample the fluid of the glove. Transfer immediately a measured volume of the sampling fluid to a test tube containing a suitable antimicrobial inactivator.

(*i*) Because contamination, product use, and enumeration are conducted sequentially within a time period of less than a day, an inactivator included in the sampling solution prior to the final wash may affect the test results. Therefore, no inactivator for the antimicrobial in the handwash formulation is to be included in the sampling solution prior to the final wash. The 50 to 100 milliliters of sampling fluid may be sufficient to dilute out the activity of the antimicrobial; however, this should be demonstrated using a procedure such as the one described in E 1054, "Test Methods for Evaluation Inactivators of Antimicrobial Agents Used in Disinfectants, Sanitizer, and Antiseptic Products," in "Annual Book of ASTM Standards," vol. 11.04, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies may be obtained from The American Society of Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and

Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(*ii*) If neutralization is not accomplished by dilution, include in the sampling solution used to collect the bacterial samples from the hand following the final wash with the test formulation an antimicrobial inactivator specific for the test formulation being evaluated.

(I) *Enumeration of bacteria in sampling solution.* (*1*) Enumerate the *Serratia marcescens* in the sampling solution using standard microbiological techniques, such as membrane filter technique or surface inoculation technique. Prepare sample dilutions in dilution fluid. Use Soybean-casein digest agar with suitable inactivator as recovery medium. The suitability of the inactivator for the antimicrobial should be demonstrated using a procedure such as described in E 1054, "Test Methods for Evaluating Inactivators of Antimicrobial Agents Used in Disinfectant, Sanitizer, and Antiseptic Products," in "Annual Book of ASTM Standards," vol. 11.04, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from The American Society of Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the **Federal Register**, 800 North Capitol St. NW., suite 700, Washington, DC. Incubate prepared plates 48 hours at 25±2 °C. Standard plate counting procedures are used to count only the red pigmented *Serratia marcescens*.

(*2*) [Reserved]

(J) *Determination of reduction.* Determine at each sampling interval changes from baseline counts obtained with test material.

(K) *Comparison with a positive control material.* (*1*) In order to validate the testing procedure, equipment, and facilities, it is required that the test formulation be compared with an active control formulation. This will require an equivalent number of panelists to be assigned to the control formulation on a random basis. All test parameters will be equivalent for both formulations, although the handwash procedure for the established formulation may be different from that of the test formulation. Both test and control formulations are to be run concurrently. The identity of the formulations used by panelists is to be blinded from those individuals counting plates and analyzing data.

(*2*) To validate the assay, compare, at each sampling interval, changes from baseline counts obtained with test material to changes obtained with control material.

(L) *Statistical analysis.* Because the hands are inoculated prior to sampling it is possible to generate counts of 1.5×10^5 to 10^6 organisms. Therefore, reductions are less variable and evaluation of the log counts using the Student's t- test or similar procedure is recommended.

(3) *Effectiveness testing of a patient preoperative skin preparation.* A patient preoperative skin preparation drug product in finished form suitable for topical applications will be recognized as effective provided that the formulated drug product at its recommended use concentration:

(i) Contains an ingredient in § 333.412 (a), (b), (c), (d), or (e).

(ii) Demonstrates in vitro activity against organisms as described in paragraph (a)(1)(ii) of this section.

(iii) When tested, in vivo, by the standard testing procedure for the evaluation of patient preoperative skin preparation drug products described in paragraph (b)(3)(iii) of this section and labeled according to § 333.460(b)(1) of this section, reduces the number of bacteria 2 $\log_{10}$ per square centimeter on an abdomen test site and 3 $\log_{10}$ per square centimeter on a groin test site within 10 minutes after product use and the bacterial cell count for each test site does not subsequently exceed baseline 6 hours after product use. When labeled according to § 333.460(b)(2) and tested, in vivo, by the standard testing procedure described in paragraph (b)(3)(iii) of this section, reduces the number of bacteria 1 $\log_{10}$ per centimeter squared on a dry skin test site within 30 seconds of product use.

(A) *Apparatus.*—(*1*) *Colony Counter.* Any of several types may be used.

(*2*) *Incubator.* Any incubator capable of maintaining a temperature of 30±2 °C may be used.

(*3*) *Sterilizer.* Any suitable steam sterilizer capable of producing conditions of sterility is acceptable.

(*4*) *Timer (stop clock).* A timer that can be read in hours and minutes.

(*5*) *Examining table.* Any elevated surface such as a 3-by- 6-foot table with mattress or similar padding to allow subject to recline.

(B) *Materials and reagents.*—(*1*) *Bacteriological pipets.* Pipets of 10.0 and 2.2 or 1.1 milliliter capacity are recommended.

(*2*) *Water-dilution bottles.* Any sterilizable glass container having a 150 to 200 milliliter capacity and tight closures may be used.

(*3*) *Scrubbing cups.* Sterile glass cylinders, height approximately 2.5 centimeter, inside diameter of convenient size to place on anatomical area to be sampled. Useful sizes range from approximately 2.5 to 4.0 centimeters. Sampling should be conducted as described in paragraph (b)(3)(iii)(J) of this section.

(*4*) *Rubber policeman.* These can be fashioned in the laboratory or purchased from most laboratory supply houses.

(*5*) *Test formulation.* Directions used to demonstrate the effectiveness of the test formulation are to be the same as those proposed for the use of the product.

(*6*) *Positive control formulation.* Any patient preoperative skin preparation formulation approved by the Food and Drug Administration is acceptable.

(*7*) *Sterile Drape or dressing.* A sterile drape or dressing should be used to cover treated skin sites.

(*8*) *Sampling solution.* Dissolve 0.4 gram potassium phosphate, monobasic, 0.1 gram sodium phosphate, dibasic and 1 gram Triton X–100 in 1 liter distilled water. Include in this formulation an inactivator specific for the antimicrobial in the test formulation. Adjust to pH 7.8 with 0.1 Normal hydrochloric acid or 0.1 Normal sodium hydroxide. Dispense 50 to 100-milliliter volumes into water dilution bottles, or other suitable containers, and sterilize for 20 minutes at 121 °C.

(*9*) *Dilution fluid.* Butterfield's phosphate buffered water adjusted to pH 7.2 and containing an antimicrobial inactivator specific for the test formulation. Adjust pH with 0.1 Normal hydrochloric acid or 0.1 Normal sodium hydroxide.

(*10*) *Plating medium.* Soybean-casein digest agar plus a suitable inactivator.

(C) *Test and control skin sites.* (*1*) The skin sites selected for use in evaluating the effectiveness of the pre-operative skin preparation are to represent body areas that are common surgical sites and are to include both dry and moist skin areas. The sites are to possess bacterial populations large enough to allow demonstrations of bacterial reduction of up to 2 $\log_{10}$ per square centimeter on dry skin sites and up to 3 $\log_{10}$ per square centimeter on moist sites. A suitable dry skin area is the abdomen and a suitable moist area is the groin. For the effectiveness testing of patient preoperative skin preparation antiseptic drug products labeled according to § 333.460(b)(2), a dry skin site such as the arm, from the shoulder to the elbow, or the posterior surface of the hand below the wrist is to be selected. The sites to be tested are to have a bacteria

population of 3 $\log_{10}$ organisms per square centimeter of skin.

(2) Treatment and control sites are to be located contralateral to each other. Each site is to be 5 by 5 centimeters.

(D) *Test panelists.* Recruit healthy adult male and female human volunteers who have no clinical evidence of dermatosis, open wounds, or other skin disorders that may affect the integrity of the study, and in sufficient numbers per formulation being tested to satisfy the statistical criteria of the clinical trial design.

(E) *Preparation of volunteers.* (1) Instruct the volunteers to avoid contact with antimicrobials (other than the test formulation) for the duration of the test. This restriction includes antimicrobial containing antiperspirants, deodorants, shampoos, lotions, soaps, and materials such as acids, bases, solvents. Bathing in chlorinated pools and hot tubs should be avoided.

(2) Volunteers are to be provided with a kit of nonantimicrobial personal care products for exclusive use during the test. Volunteers are not to shower or tub bathe in the 24-hour period prior to the application of test material or microbial sampling. Sponge baths may be taken but the skin sites to be used in the study are to be excluded.

(3) If the skin sites to be used include areas that would require shaving prior to surgery, for example, the groin site, these sites should be shaved no later than 48 hours prior to the application of test formulation or microbial sampling.

(4) After volunteers have refrained from using antimicrobials for at least 2 weeks, obtain an estimate of baseline bacterial population from one groin and one abdominal site at least 72 hours prior to entering subjects into the study. Sampling and enumeration techniques described in paragraphs (b)(3)(iii)(J) and (b)(3)(iii)(K) of this section are to be used.

(5) Based on the initial estimate of baseline bacterial population, select sufficient numbers of subjects with high bacterial counts per formulation being tested to satisfy the statistical criteria of the clinical trial design.

(F) *Study design and randomization.* Subjects admitted to the study are to be identified as to whether they meet the groin portion or abdomen portion of the study, or both. Once a subject is admitted to the study, treatments are to be randomly assigned to one contralateral groin site, for subjects identified as belonging to this study group and similar treatments are to be randomly assigned to left or right side of the abdominal area, for subjects identified as belonging to the abdominal study group. This method of choosing subjects and sampling sites fits the paired comparison statistical design. Randomization of subjects to time periods and treatment to left or right side is to be accomplished in accordance with the plan similar to that presented for surgical hand scrub products.

(G) *Number of subjects required and statistical analysis of data.* (1) Two ways to statistically evaluate effectiveness of a preoperative scrub product are presented. The first depends upon calculating the average $\log_{10}$ reduction from baseline. This is accomplished by obtaining the difference in log counts for each paired sample for each subject in the appropriate sampling time frame. This will facilitate subsequent statistical evaluation of resulting data. It is usually fairly easy to enroll subjects with counts 1×10^5 or greater when working with the groin areas. It is anticipated this method will primarily be used to evaluate data collected from the groin areas. The sample size estimation equation given earlier may be used to estimate sample sizes required for this case. Standard deviations for preoperative scrub products are relatively homogeneous when inclusion criterion require counts of 1×10^5 or greater. The standard deviations extracted from files range from 0.82 to 1.72; the median standard deviation was 0.98. When counts in the range of 1×10^5 to 1×10^6 were used, the standard deviation ranged from 0.78 to 1.22, with a median value of 0.99. Using the sample size estimation equation given in paragraph (b)(1)(iii)(F) of this section and assuming the active control preoperative scrub produces an immediate mean log reduction of 2.0 and test scrub is to be within 20 percent of this, i.e., D=0.4, and S^2=0.98, gives n=97 subjects per arm of the study. Because blocks of 6 are recommended, the sample size per treatment arm is 96 subjects.

(2) The second method for evaluating the data depends upon establishing an entry target bacterial population of greater than 250 colony forming units per square centimeter and a target reduction criterion that a successful scrub reduces bacterial counts to below 25 colony forming units per square centimeter. A successful scrub product is to provide this degree of reduction in at least 90 percent of the subjects tested. Using the normal binomial confidence interval approach, it can be shown that if the standard preoperative scrub product achieves a 90 percent success rate and it is desired to rule out success rates less than 85 percent for the new product with power of 80 percent then 340 subjects per arm are required. If it is desired to rule out success rates less than 80 percent, then the sample size is only 100 per arm. Again, since blocks of 6 or some multiple thereof, are recommended, the sample size is 102 subjects per study arm.

(3) In both cases described in paragraphs (b)(3)(iii)(G)(1) and (b)(3)(iii)(G)(2) of this section, effectiveness is judged based on calculation of 95 percent confidence intervals on the difference of the "success rate for standard scrub product minus success rate for test scrub product."

(H) *Treatment application procedure.* Apply treatment according to label directions or as stated in the proposed directions for test formulation. The control product is to be used according to the labeling directions.

(I) *Sampling schedule.* (1) For patient preoperative skin preparation antiseptic drug products labeled according to § 333.460(b)(1), the treatment is randomly assigned to one contralateral groin site and one contralateral abdominal site on each of the subjects. The assignment is to be balanced such that an equal number of right and left sites in each anatomical area receive treatment. The untreated contralateral sites serve as control sites to establish baseline populations. Collect a baseline bacterial sample from one untreated groin site and from one abdominal site on each subject using the scrub cup technique just prior to application of the preoperative skin treatment to the corresponding contralateral site. Ten minutes after treatment, sample one treated groin site and one treated abdominal site on one-third of the subjects using the same sampling technique. Thirty minutes posttreatment, sample another one-third of the subjects as before, and 6 hours posttreatment, sample the remaining one-third of the subjects.

(2) Between the time of treatment allocation and the 6-hour sampling interval, the subjects movements should be restricted. Subjects treated in the groin area should avoid activities or positions that would cause untreated skin sites to contact treated sites or clothing. Positions that might be appropriate are lying on the back or sitting with the legs extended without flexing from the trunk. To allow subjects some degree of mobility between the time of treatment and the 4-hour posttreatment sampling, the treated skin areas should be loosely draped with a sterile nonocclusive dressing. This material is to be applied in such a manner as to protect the treated skin sites from contact with untreated skin.

(3) For patient preoperative skin preparation antiseptic drug products labeled according to § 333.460(b)(2), the treatment is randomly assigned to contralateral dry skin sites on each of the subjects. The assignment is to be balanced such that an equal number of right and left sites in each anatomical area receive treatment. The untreated contralateral site serves as a control site to establish baseline populations. Collect a baseline bacterial sample from an untreated site on each subject using the scrub cup technique just prior to application of the preoperative skin preparation to the corresponding contralateral site. Thirty seconds after application, sample the treated site using the same sampling technique.

(J) *Microbiological methods.* Samples for bacterial enumeration are obtained by the detergent scrub cup technique. Hold a sterile scrubbing cup firmly to the skin. Aseptically pipet 2.5 milliliters of sterile sampling solution into the scrubbing cup and rub the skin with a sterile rubber policeman for 1 minute using moderate pressure. Aspirate the wash fluid and place in a sterile test tube. Place a second 2.5-milliliter aliquot of sampling solution in the scrub cup and rub the skin again for 1 minute with the rubber policeman. Pool the two washes and enumerate the bacteria.

(K) *Enumeration of bacteria in sampling solution.* (1) Enumerate the bacteria in the sampling solution by a standard plate count procedure such as that described in "Standard Methods for the Evaluation of Dairy Products" (available from American Public Health Association, Inc., 1015 15th St. NW., Washington, DC 20005) but using soybean-casein digest agar and a suitable inactivator for the antimicrobial where necessary. The suitability of the inactivator is to be demonstrated using a procedure such as described in E 1054, "Test Methods for Evaluating Inactivators of Antimicrobial Agents Used in Disinfectant, Sanitizer, and Antiseptic Products," in "Annual Book of ASTM Standards," vol. 11.04, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from The American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103–1187, or may be examined at the Center for Drug Evaluation and Research, 7520 Standish Pl., suite 201, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC. Prepare sample dilutions in dilution fluid. Plate in duplicate. Incubate plated sample at 30 ± 2 °C for 48 hours before reading.

(2) Determine changes from baseline counts obtained with the test material at each sampling interval for each anatomical site. For a more realistic appraisal of the activity of products, all raw data should be converted to common (base 10) logarithms. Reduction should be calculated from the average of the logarithms. This will also facilitate statistical analysis of data.

(L) *Comparison of test material with control material.* (1) In order to validate the testing procedure, equipment, and facilities, it is required that the test material be compared with an active control material. The number of test subjects will depend upon the number of control posttreatment sampling intervals chosen and the level of statistical significance desired for the test results. The identity of the formulations used by panelists should be blinded from those individuals counting plates and analyzing data.

(2) To validate the assay, compare, at each sampling interval, changes from baseline counts obtained with the test material to changes obtained with the control materials.

(c) *Effects on microbial flora.* The agency notes that, if there is some reasonable scientific indication that the activity of an ingredient will affect the microbial flora, and thereby cause a shift in the composition of this flora, e.g., an increase in the fungus or virus level that might result in greater harm, then further safety and effectiveness testing will be required.

(d) *Test modifications.* The formulation or mode of administration of certain products may require modifications of the testing procedures in this section. In addition, alternative assay methods (including automated procedures) employing the same basic chemistry and microbiology as the methods included in this section may be used. Any proposed modification or alternative assay method shall be submitted as a petition under the rules established in § 10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative assay method provides results of equivalent accuracy. All information submitted will be subject to the disclosure rules in part 20 of this chapter.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

3. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.21 [Amended]

4. Section § 369.21 *Drugs; warning and caution statements required by regulations* is amended by removing the entry for "Alcohol Rubbing Compound."

Dated: May 24, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94–14503 Filed 6–16–94; 8:45 am]

BILLING CODE 4160–01–P